U. S. TREASURY DEPARTMENT
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STUDIES ON DRUG ADDICTION

With Special Reference to Chemical Structure of Opium Derivatives and Allied Synthetic Substances and their Physiological Action

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INTRODUCTION

The studies reported in this volume have been conducted by a committee of the Division of Medical Sciences of the National Research Council. They represent a part of the unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. A complete list of the publications under the direction of this committee is appended to this volume.

The funds for the chemical studies at the University of Virginia and the pharmacological studies at the University of Michigan are provided by the Rockefeller Foundation.

The clinical work has been done under the guidance and direction of the Division of Mental Hygiene of the United States Public Health Service whose functions, as defined in law, include the administration of two Federal institutions for the confinement and treatment of persons addicted to the use of habit-forming drugs; the conduct of studies dealing with the nature of drug addiction and the best methods of treatment and rehabilitation of persons addicted to the use of habit-forming drugs; the dissemination of information on methods of treatment and research in this particular field; the cooperation with State and local jurisdictions and other agencies, with a view to their providing facilities for the care and treatment of narcotic addicts; and the supervising and furnishing of medical and psychiatric services in the Federal prison system. These functions also include studies and investigations of the abusive uses of narcotic drugs and the quantities necessary to supply the normal and emergency medical and scientific requirements of the United States and studies and investigations of the causes, prevalence, and means for the prevention and treatment of nervous and mental diseases.

The purpose of these studies is to find, if possible, some means of reducing or correcting the evils of drug addiction. It was recognized that the problem had reached a point in international and national affairs which demanded attention and a very considerable expenditure. Although a relatively small proportion of those who receive morphine for various reasons develop addiction, it would seem as if there must be a receptor in certain individuals which gives rise to a sense of euphoria when combined with a chemical unit of, for instance, the morphine molecule. The majority of those who for various reasons are given morphine do not attain this sense of euphoria and

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therefore are not tempted to seek repetition of its administration nor to become addicted to its use.

In determining its program the committee was influenced by the rapid decline in the use of cocaine as an addiction drug after the discovery of novocaine and pantocaine and by the fact that addiction is not considered to be associated with the isoquinoline derivative of opium but with the phenanthrene derivatives of the morphine type. It was, therefore, decided to proceed along the lines of separating chemically, if possible, the addiction property of morphine from its other more salutary attributes. The committee thought, if this could be done, the same result might follow as occurred with cocaine. Or if such substances could be produced synthetically, the same result might be attained and much might have been done to lessen the danger and importance of drug addiction.

The committee realized, however, that if this were finally accomplished it would raise in many countries in the world a labor problem among those now engaged in the cultivation of the poppy plant. This economic aspect of the problem has already been considered by numerous surveys conducted abroad, having for their object the replacing of poppy cultivation with other crops in those countries in which poppy cultivation was a major industry. Morphine is by no means the ideal analgesic because of its emetic action and respiratory effect. If the ideal drug is derived from morphine this problem would not arise but if it is derived from coal tar the world would have to face it.

While the committee was not sure of accomplishing its purpose it felt perfectly sure that, by a systematic study of a series of modifications of the morphine molecule, to be followed by a careful physiological study and application to man of those substances which gave definite indications of value, it would add greatly to our knowledge of animal and human physiology and furnish the base line for future studies in this field. The committee realized that, since man presents practically the only problem of addiction and since the results from the studies of these drugs in animals cannot be directly applied to man, the final studies must always be in man himself.

A series of 16 drugs, all modifications of the morphine molecule and of known chemical composition, with morphine as a base line, ranging from codeine to beta-chloromorphide, have been studied in man. One of the chemical difficulties in this research has been to provide drugs which would prolong the pain control factor so as to reduce the need for repeated dosage and at the same time to eliminate the fraction responsible for euphoria. At the present time it appears that rapidity of action of a drug has a direct relation to its continuance of action. The more rapid the action the shorter is the duration of its effect. This property possibly has a relation also to its euphoria attribute.

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It has been possible to produce by synthesis from coal tar derivatives drugs that are in animals the equal of codeine or pseudocodeine in the control of pain and which have no euphoric quality. Only a few of the synthetic drugs so far have been tried in man for various reasons, such as toxicity and solubility, but there is hope of ultimate success in this field. Important progress has already been made both in the analytical and synthetic sides of this method of approach. The intention of the present publication is to bring the results of these studies up to date and make them available to the rest of the world.

A new implement has recently been added for the study of these drugs in man. The United States Public Health Service, through the Division of Mental Hygiene, has just provided the most sensitive encephalograph yet built, at the United States Public Health Service Hospital at Lexington, Ky. The early studies with this instrument indicate that for the first time an objective method has been provided for the differentiation of the action of a series of addiction drugs of known chemical modification in the study of brain physiology. In a single case a difference has been found in the encephalograms after the administration of morphine and the methyl ether of morphine (codeine).

The encephalograph is only one of the methods which have been provided at Lexington for the study of drug addiction by a group of experts in a well-rounded plan. In no other country does such an institution exist and it would not be possible for the National Research Council to undertake its work without the sympathy and full cooperation of this great clinical facility. Studying drug addiction in other institutions often fails because of the short stay and lack of supervisory control over the group of patients with whom such a study must be carried on.

There does not exist today a satisfactory base line for the study of pain control in man because of the wide differences in the response to pain in different individuals. A method, using nerve conduction as an index, is being worked out at Lexington. This, if accomplished, will facilitate this work. The method assumes that the sensitiveness of a nerve trunk in conduction will be an index of its ability to transmit all sensation, including pain.

Other clinical studies are being carried out by the department of public health of the State of Massachusetts in cooperation with the Division of Mental Hygiene of the United States Public Health Service and in the departments of medicine and surgery of the University of Michigan Medical School at Ann Arbor.

It is hoped that the publication of these studies at this time will be of value not only to those interested in drug addiction but also to chemists, clinicians, physiologists, pharmacologists, and all who

are interested in the question of the relationship between chemical structure and pharmacological action in animals and man.

In addition, the products of the chemical laboratory of the University of Virginia have found experimental application by workers in the sex hormones, tissue culture, and carcinogenic activity. Furthermore the divisions of chemistry and pharmacology have provided training in fields for which no other institutions here in the United States are prepared. Already the University of Virginia has had to yield nine men to the industries in the United States and elsewhere.

It is to be remembered that the problem of drug addiction is only part of the far greater problem of mental health which in all its branches is probably the most serious welfare problem with which the country has to deal.

The committee wishes to express its appreciation to all who have taken part in this coordinated study which has provided a new and so far successful method of approach to a very difficult problem.

The Committee is especially indebted to Dr. Walter L. Treadway, Assistant Surgeon General in charge of the Division of Mental Hygiene, U. S. Public Health Service, for his valuable assistance in helping to coordinate the various interests of many diversified agencies of government that are concerned with many aspects of the problem of drug addiction, and for his cooperation in helping to make available technically trained personnel and equipment in connection with the clinical studies herein reported.

WM. CHARLES WHITE,
Chairman, Committee on Drug Addiction.

WASHINGTON, D. C., *December 6, 1937.*

CONTENTS

	Page
Introduction	iii
PART I. SOME RELATIONSHIPS BETWEEN CHEMICAL CONSTITUTION AND PHARMACOLOGICAL ACTION IN THE MORPHINE SERIES	
Introduction	1
1. The Phenolic Hydroxyl Group	4
a. The isomers of morphine and dihydromorphine	4
b. The alcoholic ethers of morphine and γ-isomorphine types	9
c. The alcoholic esters of morphine and its isomers	10
d. The desoxymorphines	11
e. The halogenomorphides	12
2. The Alcoholic Hydroxyl Group	13
a. Changes in position or configuration	13
b. Muzzling the alcoholic hydroxyl	17
c. Replacement of the secondary alcoholic group by ketonic oxygen	20
d. Replacement of the alcoholic hydroxyl by hydrogen	21
e. Replacement of the alcoholic hydroxyl by halogen	21
f. Replacement of the alcoholic hydroxyl by basic groups	21
3. The Ether Oxygen Bridge	25
4. The Alicyclic Unsaturated Linkages	26
5. The Influence of Nuclear Substituents	29
6. The Change From Tertiary to Quaternary Nitrogen	33
Conclusions	34
References	35
PART II. ATTEMPTS TO SYNTHESIZE SUBSTANCES WITH CENTRAL NARCOTIC AND, IN PARTICULAR, ANALGESIC ACTION	
Introduction	37
1. Phenanthrene, Hydrogenated Phenanthrenes, and Simple Derivatives	42
a. Phenanthrene and its hydro derivatives	42
b. Monohydroxyphenanthrenes	47
c. Polyhydroxyphenanthrenes and hydroxyphenanthrylene oxides	48
d. Amino- and aminomethyl-phenanthrenes	51
e. Amino derivatives of dihydro- and tetrahydro-phenanthrenes	54
f. Hydroxyaminophenanthrenes	58
g. Aldehydes, ketones, and carbinols of phenanthrene and hydrophenanthrenes	61

1. PHENANTHRENE, HYDROGENATED PHENANTHRENES, AND SIMPLE DERIVATIVES—Continued. Page

h. Hydroxyacetylphenanthrenes and cyclic ketones of tetrahydro- and octahydro-phenanthrenes 63

i. Phenanthroic acids, phenanthryl propionic acid, and derivatives 66

Summary 69

2. AMINO ALCOHOL DERIVATIVES OF PHENANTHRENE AND HYDROPHENANTHRENES 72

a. Amino ketones and amino alcohols of the ethanolamine type 72

b. Amino alcohols of propanolamine types 76

c. Phenolic amino alcohols 79

d. Amino alcohols derived from 9, 10-dihydrophenanthrene 81

e. Amino alcohols derived from symmetric octahydrophenanthrene 85

f. Cyclic amino alcohols derived from tetrahydrophenanthrene 88

g. Homologous cyclic amino alcohols derived from tetrahydrophenanthrene 92

Summary 95

3. DERIVATIVES OF OTHER CONDENSED RING SYSTEMS 97

a. Dibenzofuran, tetrahydrodibenzofuran, and simple amino, carbonyl, and carboxyl derivatives 97

b. Amino ketones and amino alcohols derived from dibenzofuran 99

c. Benzofuroquinolines (pyridinodibenzofurans) 101

Summary 102

d. Carbazole, aminocarbazole, and derivatives 103

e. Amino- and hydroxy-tetrahydrocarbazoles and an amino alcohol derived from carbazole 106

Summary 109

Conclusions 110

References 112

PART III. CLINICAL STUDIES OF DRUG ADDICTION, WITH SPECIAL REFERENCE TO OPIUM DERIVATIVES AND ALLIED SYNTHETIC SUBSTANCES

1. INTRODUCTION 114

2. DEFINITIONS 115

3. ADDICTION LIABILITY STUDIES 116

a. Methods 116

b. Results 120

c. Discussion 125

4. PHARMACOLOGIC CLINICAL STUDIES 127

5. CONCLUSIONS 128

6. REFERENCES 128

LIST OF PUBLICATIONS OF THE COMMITTEE ON DRUG ADDICTION, NATIONAL RESEARCH COUNCIL, 1930–37 131

INDEX 139

PART I. SOME RELATIONSHIPS BETWEEN CHEMICAL CONSTITUTION AND PHARMACOLOGICAL ACTION IN THE MORPHINE SERIES

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Introduction

The investigations summarized in this communication form a part of the research program begun in 1929 under the auspices of the Committee on Drug Addiction of the National Research Council. This program has as its primary object the synthesis of drugs having little or no tendency to cause addiction, which may serve to replace morphine, heroin, and other dangerous narcotics in their therapeutic applications. The results so far obtained in this systematic search for an "ideal narcotic" are scattered through a long series of papers in the chemical, pharmacological, and clinical journals, as well as in unpublished reports to the National Research Council, and the present paper is intended to coordinate and review the accumulated data on the problem.

In approaching the synthesis of new drugs that shall exert a morphine-like action, two routes are open, namely, operation upon the alkaloids of promising structural type, especially those of the morphine group, or syntheses starting with unrelated or distantly related nuclei. The first method, while likely to lead to active drugs, has the disadvantage that products with activity comparable to that of morphine may be likewise addicting. However, because of the ease

with which a large variety of structural changes may be effected in the alkaloids of the morphine series, and the general high activity of the derivatives, much valuable information concerning the pharmacological significance of these changes may be obtained. The second method has the obvious disadvantage that the possible starting materials and the directions in which synthesis may be undertaken are multitudinous, and there appears to be no previous experience in this connection beyond isolated haphazard experiments.

Whether it will be possible to prepare any drug with the power to control pain requisite for a morphine substitute, without at the same time introducing factors which will cause the appearance of other phenomena leading to addiction, is a point which remains to be settled. The most useful effect of morphine (and certain of its derivatives), its unrivalled ability to alleviate pain through its action on the central nervous system, is accompanied by numerous other, often medically undesirable, actions in the body. These are, briefly, respiratory, circulatory, gastro-intestinal, emetic, and general depressant manifestations. In addition, the administration of morphine in many individuals not only relieves the discomfort of pain and restlessness, but also causes a pleasurable feeling of well-being, a "euphoria." Both the relief of discomfort and the euphoria may lead to repeated administration and repeated administration sooner or later leads to dependence, the *sine qua non* of addiction. This dependence is physical as well as mental, and although the mechanism of its development is obscure, it is probable that there is a relationship between it and the chemical structure of the addicting agent of the morphine series. The development of dependence after prolonged administration appears to be related to the presence of certain modifiable peripheral groups rather than to the structural skeleton of the morphine molecule itself. The numerous morphine derivatives containing the complete morphine carbon-nitrogen-oxygen skeleton whose addiction liability is in some measure known, vary so greatly in the intensity of this factor that it seems improbable that the structural skeleton itself is a decisive element in the development of dependence. In addition, there is direct evidence that the physiological effects of a particular drug, in part at least, result from the presence of various functional groups, since, by suitable chemical changes in these groups, characteristic morphine actions can be changed and often in a predictable direction. Therefore, it seems reasonable to expect that addiction also may be dependent upon functional groups and hence may be modified by chemical changes. Even though it has been possible in many cases to associate the intensity of a given action, analgesia for example, with the modification of definite groups in the molecule, a similar association between such groups and addiction has not yet been demonstrated. The

most promising advance in this direction appears to be the discovery that it is possible to achieve in certain drugs a marked dissociation of duration of analgesia and duration of dependence satisfaction, and it is probable that the most desirable type of drug from the standpoint of addiction liability will be one in which duration of analgesia exceeds by a wide margin duration of dependence satisfaction.

It should be pointed out that the hypothesis of the relationship between chemical structure and pharmacological action, including addiction, may be expressed in a somewhat different form. The many characteristic actions of the narcotic may be considered to be functions of the structural skeleton, but their exhibition in any given example requires the presence of specific peripheral groups, these acting as points of contact or reactive mechanisms for the living cell systems concerned. According to this hypothesis also, appropriate chemical modification of peripheral groups would modify the characteristic morphine actions, again including the power to cause addiction.

The selection of compounds for clinical trial and addiction studies has been made on the basis of pharmacological experiments covering about 125 morphine derivatives, most of which were prepared for the first time in connection with this work. We have regarded it as of primary importance to choose for the pharmacological tests types of compounds that will demonstrate the physiological significance of the various peripheral groups of the morphine molecule, and to study the changes produced in the physiological picture through changes in the nature or position of such groups on the nucleus. From such studies has been gained not only a knowledge of the influence of these groups on the action of drugs of the morphine series, but also information of value in the synthesis of compounds from the phenanthrene, phenanthrylene oxide, dibenzofuran, phenanthridine, and carbazole series. The relationships between constitution and physiological action that have been found to exist in these synthetic substances will be discussed in the following communication; for the present it may be stated that many of the conclusions drawn from the behavior of related drugs in the morphine series appear to be applicable to similarly related derivatives of the phenanthrene and dibenzofuran series.

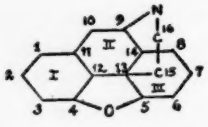
The methods employed in the pharmacological experiments have been fully described elsewhere (*1*, *2*, *3*, *4*, *5*, *6*). The routine points of comparison were toxicity (mice), convulsant action (mice, principally), general depressant effect (rats, chiefly), analgesia (cats), exciting effect (cats), emetic action (cats), and respiratory effect (rabbits). In many instances other phenomena have been studied, particularly gastro-intestinal action. The effects thus observed, ar-

ranged according to the changes in chemical structure in the morphine group, will be discussed under the following general divisions:

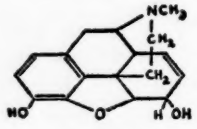
1. The phenolic hydroxyl group.
2. The alcoholic hydroxyl group.
3. The ether oxygen bridge.
4. Alicyclic unsaturated linkages.
5. The influence of nuclear substituents.
6. The change from tertiary to quaternary nitrogen.

1. The Phenolic Hydroxyl Group

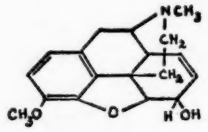
It has long been known that methylation of the phenolic hydroxyl group of morphine (II) results in a product (codeine, III) in which the pharmacological activity of morphine has on the whole been greatly diminished. In addition to the methyl ether, the ethyl and benzyl ethers of morphine (Dionin and Peronin) have been previously investigated, but the effect of etherification (or esterification) of the phenolic hydroxyl in compounds of the group other than morphine



I. Numbering system.



II. Morphine.



III. Codeine.

itself, has been practically neglected. In the present studies, the result in pharmacological action of this type of change will be considered for all of the important known types of morphine derivatives.

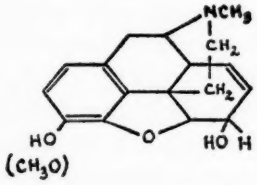
(a) THE ISOMERS OF MORPHINE AND DIHYDROMORPHINE

When morphine is treated with reagents suited to replace the alcoholic hydroxyl group by chlorine, as phosphorus trichloride, or thionyl chloride, isomeric chloromorphides, designated as α- and β-, are formed. From the action of phosphorus tribromide, a bromomorphide is obtained.

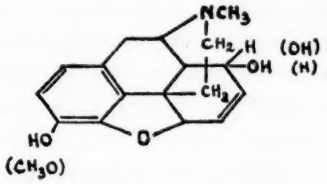
Hydrolysis of any of the halogenomorphides with dilute acetic acid yields, in varying amounts, three isomers of morphine, but no morphine. α-Isomorphine is a diastereomer of morphine, a derivative in which the alcoholic hydroxyl group at position-6 is reversed in configuration, without other changes in the molecule (formula IV); β- and γ-isomorphines differ from each other similarly in the configuration of the alcoholic hydroxyl, which in this pair is located at position-8, with the unsaturation at 6, 7 (*7*). These two are, of course, structural isomers of morphine and α-isomorphine.

The respective methyl ethers corresponding to the α-, β-, and γ-isomorphines are isocodeine, allopseudocodeine, and pseudocodeine, which may be prepared either by hydrolysis of the halogenocodides, or by methylation of the morphine isomers at the phenolic group. The ethyl ethers of the morphine isomers have been prepared only by ethylation of the phenolic group in the isomers themselves (*8*).

The isomers of dihydromorphine and dihydrocodeine cannot be obtained by hydrolysis of chlorodihydromorphide or chlorodihydrocodide, for these halogeno derivatives resist hydrolysis, and, were hydrolysis possible, lack the alicyclic double linkage whose presence is necessary for the α, γ-shift that results in the 8-hydroxy types in the unhydrogenated series. The isomeric members of the dihydro series must therefore be prepared by reduction of the isomers themselves. α-Isomorphine and isocodeine can be hydrogenated with ease, to give the diastereomers of dihydromorphine and dihydro-



IV. α-Isomorphine (and Isocodeine).

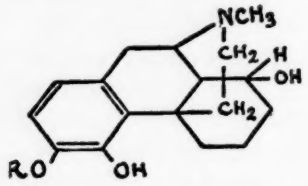


V. β- and γ-Isomorphines (and Allopseudo- and Pseudo-codeine).

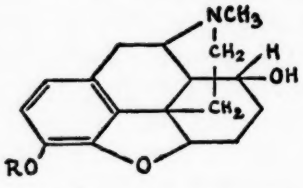
codeine, respectively, but β- and γ-isomorphines and their methylated analogs, because of the allyl ether system present (-O-CH-CH=CH-), can be converted to the dihydro series only by the application of special hydrogenation methods. Under the ordinary conditions of catalytic hydrogenation, as base in organic solvents, or as salts in aqueous solution, β- and γ-isomorphines, and allopseudocodeine and pseudocodeine react with two moles of hydrogen, whereby the alicyclic double bond is saturated and the oxide ring is opened reductively, with formation of a new phenolic hydroxyl (*9*, *10*).

The tetrahydro derivatives (VI, R=H; VI, R=CH_3) are thus obtained almost exclusively. When the hydrogenation is carried out in the presence of a large excess of mineral acid, or preferably with the alkaloid hydrochloride in glacial acetic acid, scission of the oxide ring can be largely suppressed, and the normal dihydro derivatives (VII, R=H or CH_3) are obtained in yields up to 80 percent of the theoretical amount. The remainder of the material appears as the tetrahydro derivative. This method of controlled hydrogenation has been applied successfully so far to the following 6, 7-unsaturated derivatives: pseudocodeine (*11*), allopseudocodeine (*12*), β-isomor-

phine (*13*), γ-isomorphine (*10*), pseudocodeine methyl ether (*14*), γ-isomorphine alcoholic methyl ether (*8*), γ-isomorphine alcoholic ethyl ether (*8*), pseudocodeinone (*15*), ε-methylmorphimethine (*11*), desoxymorphine-C (*16*), desoxycodeine-C (*16*), and 8-piperidocodide (*17*).



VI. Tetrahydro 8-hydroxy type.



VII. Dihydro 8-hydroxy type.

In each of the tables of this report (except number 20) all of the figures are milligrams of alkaloidal base per kilogram. Their connotation and derivation is as follows: *Toxicity*=average fatal dose, amount killing 50 percent or more of animals used, administered subcutaneously to mice; *convulsant action*=the smallest amount with which convulsions were observed during the determination of the average fatal dose in mice; *general depression*=smallest dose preventing immediate righting of at least 75 percent of a group of 20 rats, 30 minutes after intraperitoneal injection; *analgesia*=amount of substance administered intramuscularly which caused in at least four of the five cats receiving the dose an increase in the pressure required to evoke a response when applied to the terminal portion of the tail; *exciting effect*=smallest dose with which definite signs of exciting action were seen in at least two of a group of five cats; *emetic action*=smallest dose with which a cat vomited, or in many instances, when no dose used caused vomiting, the smallest dose with which nausea, licking with or without salivation, occurred; *respiratory effect*=minimal effective depressant dose (minute volume). See reference (*6*) for derivation of this figure. A great part of the data summarized in these tables is from the unpublished protocols of work in progress in the Pharmacological Laboratory of the University of Michigan. This is indicated by a double asterisk after the name of the substance. References to published results are given after the heading of a table. New substances, made for the first time in connection with this work, are marked with an asterisk before the laboratory sample number.

TABLE 1.—*Methyl substitution of the phenolic hydroxyl of morphine, dihydromorphine, and their isomers (6, 18, 19, 20)*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine	531/241	531/161	6.75/36.1	0.75/8.04	0.57/8.04	0.22/16.0+	0.15/1.3
2. Codeine							
37. Dihydromorphine	133/225	(a)/168	17.7/14.1	0.26/7.20	1.77/6.45	0.17/3.22+	0.11/0.9
20. Dihydrocodeine							
236. α-Isomorphine	890/589	(b)/589	22.2/58.9	0.80/13.0	0.89/13.0	0.13/(c)	0.15/1.5
36. Isocodeine							
*265. Dihydro-α-isomorphine	890/896	(d)/(c)	22.2/29.8	0.80/1.91	0.80/0.98	0.18/0.98+	0.13/0.22
51. Dihydroisocodeine							
140. β-Isomorphine	324/267	324/178	74.0/80.1	10.1/13.3	9.26/26.7	4.63/13.3+	2.14/(f)
64. Allopseudocodeine							
*266. Dihydro-β-isomorphine	152/392	152/325	22.2/74.1	3.11/7.09	4.45/7.09	0.89/9.27+	0.26/2.0
*165. Dihydroallopseudocodeine							
141. γ-Isomorphine	2000+/1780	(g)/(c)	133+/89.1	7.09/17.8	7.09/22.2	1.77/4.45	2.36/48.0
3. Pseudocodeine							
*158. Dihydro-γ-isomorphine	1687/975	(g)/(g)	133+/110.2	4.44/4.24	8.87/16.9	2.66/3.39	1.45/49.0
*99. Dihydropseudocodeine							

*New substance. (Single asterisk (*) has same significance in subsequent tables.)
+After emetic dose indicates that vomiting did not occur with any dose used; nausea (licking, with or without salivation) seen at dose indicated.
[a] Convulsions infrequent with fatal doses.
[b] Convulsions do not always occur with fatal doses.
[c] None with 6 to 16 mg per kg.
[d] Convulsions rarely occur with fatal doses; never with recovery.
[e] With fatal doses twitching of muscles, slight increase in reflexes, but no convulsions.
[f] Up to 30 mg per kg there is no significant effect on respiratory rate or tidal volume.
[g] Neither increase in reflexes nor convulsions have been seen.

Methylation of the phenolic hydroxyl of the morphine isomers generally increased toxicity and convulsant action, the increase in the latter being indicated either by a smaller percentage of the fatal dose causing convulsions or by a greater incidence of convulsions with fatal doses. Perhaps one should class as an exception the failure of convulsions or even of increased reflexes to appear with the methyl derivative of γ-isomorphine or of dihydro-γ-isomorphine, both of which seemed to be purely depressant in mice. In view of this fact it is perhaps remarkable that the minimal effective depressant dose for the rat is so high, but in this group, with each substance in which the alcoholic hydroxyl was attached to the 8-carbon, whether toxic doses seemed to be depressant only or exhibited convulsant action also, relatively large amounts of the drug were needed to depress the righting reflex of the rat.

Almost invariably, all of the typical morphine-like effects except convulsant action were decreased by methylation of the phenolic hydroxyl. The decrease was most marked and most consistent where quantitative evaluation of the effect is most exact, namely, respiratory and analgesic effects.

In regard to intestinal activity (dog), morphine was about twelve times as effective as codeine in reducing rhythmic frequency, and six

or more times as effective in increasing tone (*2*). Through the remainder of the group of isomers the codeine members had less effect on intestinal activity than their morphine relatives, but an exact statement of quantitative relationships cannot be made at this time.

Again, in cats 1.0 mg per kg of codeine injected intravenously had less effect on blood pressure than 0.1 mg per kg of morphine (*21*). The former produced an average fall of only 7.5 mm, the latter an average fall of 11.2 mm. Circulatory studies with the isomers of codeine will be referred to later.

TABLE 2.—*Ethyl and benzyl substitution of the phenolic hydroxyl (22, 23)*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine	531/136	531/122	6.75/42.6	0.75/7.66	0.57/17.0	0.22/8.5+	0.15/0.48
82. Ethylmorphine**							
236. α-Isomorphine	890/750	(a)/(b)	22.2/(c)	0.80/5.00	0.89/(d)	0.13/2.00	----------
*300. Ethyl-α-isomorphine**							----------
*265. Dihydro-α-isomorphine	890/331	(e)/(f)	22.2/47.3	0.80/2.83	0.80/2.83	0.18/2.36	----------
*301. Ethyldihydro-α-isomorphine**							----------
141. γ-Isomorphine	2000+/1157	(b)/(b)	133+/100+	7.09/10.7	7.09/(g)	1.77/1.79	----------
*298. Ethyl-γ-isomorphine**							----------
*158. Dihydro-γ-isomorphine	1687/1200	(b)/(b)	133+/100+	4.44/5.00	8.87/20.0	2.66/2.00	----------
*299. Ethyldihydro-γ-isomorphine**							----------
1. Morphine	531/35	531/35	6.75/(h)	0.75/7.87	0.57/7.87	0.22/8.74	0.15/(i)
305. Benzylmorphine**							
37. Dihydromorphine	133/35	(j)/35	17.7/(k)	0.26/2.40	1.77/2.18	0.17/1.74	0.11/(l)
*306. Benzyldihydromorphine**							
111. Heterocodeine	72/28	65/28	1.40/23.9	0.48/3.99	0.32/(d)	2.40+/7.99+	0.016/0.20
*393. Benzylmorphine methyl ether.**							
*126. Dihydrodesoxymorphine-D	104/55	104/55	0.32/6.36	0.08/1.59	0.16/0.81	(m)/0.90+	0.012/0.27
*312. Benzyldihydrodesoxymorphine-D.**							
37. Dihydromorphine	133/107	(j)/107	17.7/32.8	0.26/1.64	1.77/8.21	0.17/0.82	0.11/0.16
*316. Methoxymethyldihydromorphine.**							

**Data from work in progress, unpublished. (Double asterisk (**) has same significance in subsequent tables.)

[a] Convulsions do not always occur with fatal doses.

[b] Neither increase in reflexes nor convulsions have been seen.

[c] 3 of 10 rats receiving 70 mg per kg had convulsions and died; the righting reflex was not depressed by smaller doses.

[d] No trace of exciting effect up to 10 mg per kg.

[e] Convulsions rarely occur with fatal doses, never with recovery.

[f] Occasional twitching; rarely hyperirritability during recovery; no convulsions.

[g] No excitement up to 20 mg per kg.

[h] Three rats receiving 20 mg per kg had convulsions and 2 died; smaller doses did not depress the righting reflex.

[i] Up to 20 mg per kg no significant effect on respiratory rate or minute volume.

[j] Convulsions infrequent with fatal doses.

[k] M. E. D. 21.8; convulsions did not occur nor death until a dose of 35 mg per kg was reached.

[l] With 20 mg per kg minute volume 80 percent of normal (average of 10 animals); with 40 mg per kg minute volume 110 percent of normal (reflex activity increased); doses less than 10 mg per kg had no significant effect on respiratory rate or minute volume.

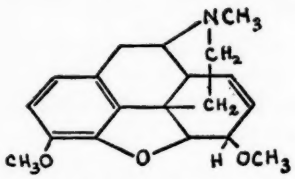
[m] No emetic effect up to 1.0 mg per kg. See reference (*23*) for emetic effect with repeated administration.

If the phenolic hydroxyl of morphine and its isomers was covered with an ethyl or benzyl group instead of a methyl, the same change in

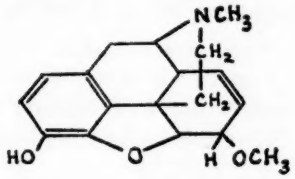
pharmacological activity was effected, toxicity and convulsant action were increased and the other effects were decreased (table 2). The low grade exciting effect in cats and the high doses required to depress the righting reflex in rats (sometimes closely approaching the fatal dose) were particularly striking. Generally speaking, the ethyl derivatives were more emetic than the methyl.

(b) THE ALCOHOLIC ETHERS OF MORPHINE AND γ-ISOMORPHINE TYPES

The alkylation of the secondary alcoholic hydroxyl group present in the isomeric codeine types can be accomplished by protecting the tertiary nitrogen atom (conversion to the N-oxide) and subjecting the compound to the prolonged alkylation treatment of Pschorr (*24*). Similarly, it is possible to etherify the alcoholic hydroxyl group alone in the isomeric morphine types by protecting both the phenolic hydroxyl and the tertiary nitrogen atom with groups which can later be removed (method of C. Mannich (*25*) see page 17). The codeine



VIII. Codeine Methyl Ether.



IX. Morphine Alcoholic Methyl Ether (Heterocodeine).

alcoholic ethers are of the type VIII, the morphine alcoholic ethers (also named as heterocodeines) are of type IX.

TABLE 3.—*Substitution of the phenolic hydroxyl in alcoholic ethers of morphine and γ-isomorphine types*

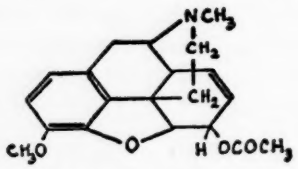
	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
111. Heterocodeine	72/160	65/141	1.40/12.0	0.48/6.00	0.32/6.00	2.40+/9.00+	0.016/0.5
85. Codeine methyl ether							
*112. Dihydroheterocodeine	71/117	71/105	1.70/12.4	0.17/1.16	0.17/1.16	0.17+/7.76+	0.019/0.2
87. Tetrahydrothebaine							
*303. γ-Isomorphine alcoholic methyl ether**	624/459	624/321	16.9/75.0	3.12/8.34	2.89/16.6	2.89+/8.34+	0.19/4.42
91. Pseudocodeine methyl ether							

In the alcoholic ether group (table 3) the methyl derivatives were not more toxic, but convulsant action is seen to be increased if one compares in each instance the percentage of the fatal dose with which

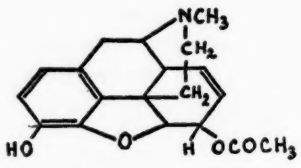
convulsions occurred. The appearance of marked convulsant action with pseudocodeine methyl ether is especially noteworthy since almost all of the 8-carbon derivatives of the γ-isomorphine type were nearly or entirely nonconvulsant. As in group (a) (tables 1 and 2), here again the other morphine-like effects were definitely decreased.

(c) THE ALCOHOLIC ESTERS OF MORPHINE AND ITS ISOMERS

The alcoholic hydroxyl group in codeine or dihydrocodeine, and their isomers, is easily esterified. For this purpose, the use of acetic anhydride in pyridine is most advantageous. For comparison with acetylcodeine and its isomers, the monoacetylmorphines were prepared by acetylating both hydroxyl groups of morphine and its isomers, and



X. Acetylcodeine.



XI. Monoacetylmorphine.

subsequently hydrolyzing the phenolic acetyl group alone with cold hydroxylamine hydrochloride solution.

TABLE 4.—*Substitution of the phenolic hydroxyl of alcoholic esters of morphine and its isomers* (*27*)

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action
199. Monoacetylmorphine	293/99	180/60	0.9/18.0	0.18/9.03	0.18/7.22	0.18+/4.51+
366. Acetylcodeine**						
*129. Monoacetyldihydromorphine	99/91	89/91	11.7/27.0	1.35/4.52	1.35/9.04	0.90/3.63+
367. Acetyldihydrocodeine**						
*375. Monoacetyl-α-isomorphine**	144/112	89/67	1.0/8.92	0.18/3.72	0.09/2.23	[a]/[b]
*318. Acetylisocodeine**						
*376. Monoacetyl-β-isomorphine**	338/429	270/322	120+/120+	22.5/50.0+	27.0/[c]	9.00/27.0
*368. Acetylallopseudocodeine**						
*377. Monoacetyl-γ-isomorphine**	428/750	342/413	22.0/70.0	2.70/10.0	1.80/[d]	4.5+/8.0+
389. Acetylpseudocodeine**						

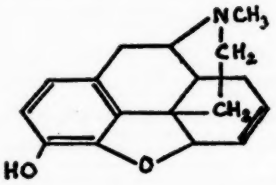
[a] Brief nausea in only 3 of 45 animals with doses of 0.05 to 1.0 mg per kg—once with 0.1, once with 0.5, and once with 1.0 mg.
[b] Brief nausea in only 2 of 35 animals with doses of 0.5 to 5.0 mg per kg—once with 4.0 and once with 5.0 mg.
[c] No apparent exciting effect up to 50.0 mg per kg.
[d] None up to 15.0 mg per kg.

The methylation of the alcoholic esters of morphine (table 4) and its isomers did not always increase toxicity or convulsant action. Unfortunately the data for the other effects are not yet complete but it is

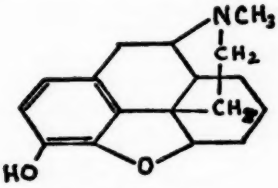
apparent from the figures available that the analgesic, exciting, and emetic actions were decreased in the methylated compounds.

(d) THE DESOXYMORPHINES

The desoxymorphines and desoxycodeines differ from morphine and codeine in empirical formula by an oxygen atom, i. e., in that the

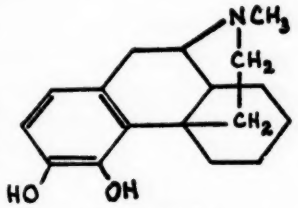


XII. Desoxymorphine-C.



XIII. Dihydrodesoxymorphine-D.

alcoholic hydroxyl group has been replaced by a hydrogen atom. There is, however, no member of the unhydrogenated series in which this is the sole change. Desoxymorphine-C and desoxycodeine-C are obtained by elimination of hydrogen chloride from chlorodihydromorphide or chlorodihydrocodide, and have a pseudocodeine type of structure (XII) (*16*, *28*).



XIV. Tetrahydrodesoxymorphine.

This type of desoxymorphine derivative, because of the position of the double bond, undergoes normal hydrogenation only under special conditions, so that the preparation of the corresponding dihydrodesoxymorphine-D ("Desomorphine") and dihydrodesoxycodeine-D ("Desocodeine") is more easily accomplished starting from the halogenomorphides or halogenocodides (*29*, *30*). The hydrogenation of these compounds, depending upon the conditions, may proceed almost entirely in the direction of the desired dihydrodesoxy derivatives, or may yield tetrahydrodesoxymorphine (XIV) or tetrahydrodesoxycodeine, which thus also are available for comparison of the effect of methylation.

TABLE 5.—*Substitution of the phenolic hydroxyl of the desoxymorphine series*

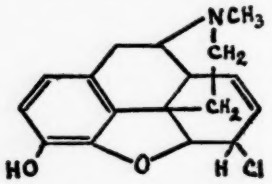
	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
*68. Desoxymorphine-C	79/110	79/(a)	0.52/6.00	0.45/1.00	0.45/1.00	0.90+/5.00+	0.016/0.09
67. Desoxycodeine-C							
*126. Dihydrodesoxymorphine-D	104/131	104/65	0.32/2.12	0.08/1.96	0.16/1.96	(b)/0.65+	0.012/0.08
16. Dihydrodesoxycodeine-D							
*126. Dihydrodesoxymorphine-D	104/55	104/55	0.32/6.36	0.08/1.59	0.16/0.81	(b)/0.90+	0.012/0.27
*312. Benzyldihydrodesoxymorphine-D**							
*55. Tetrahydrodesoxymorphine	221/133	(c)/133	14.0/35.4	0.62/4.43	1.86/6.67	6.20+/2.21+	(d)/(e)
54. Tetrahydrodesoxycodeine							

[a] With No. 68 reflexes are increased slightly and convulsions occur in some animals with fatal doses; with No. 67 reflexes are exaggerated and convulsions occur in all animals with fatal doses.
[b] No emetic effect up to 1.0 mg. per kg. See reference (*23*) for emetic effect with repeated doses.
[c] Brief convulsive movements on stimulation with fatal doses. With No. 54 reflexes are exaggerated and convulsions occur spontaneously, as well as in response to stimulation, with fatal doses.
[d] Effective dose probably between 1.0 and 2.0 mg per kg.
[e] Effective dose probably not less than 10.0 mg per kg.

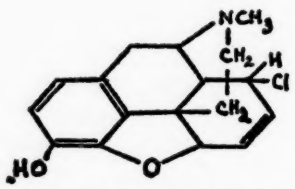
Again we find (table 5) the same modification of pharmacological action as in the previous groups, the only exception being the occurrence of nausea with smaller doses in three instances of the codeine type of compound.

(e) THE HALOGENOMORPHIDES

The isomers, α- and β-chloromorphide, or their methyl ethers, α- and β-chlorocodide, are obtained when any of the four isomeric morphines or codeines, respectively, are treated with phosphorus chlorides or thionyl chloride. The nature of the isomerism is still uncertain. In α-chloromorphide and α-chlorocodide, the halogen atom is known to be at the 6-position (*31*), but its configuration, whether of the codeine or the isocodeine type, cannot be determined. In the β-series, which may be prepared most easily by rearrangement of the α-series, the halogen atom is believed, without convincing evidence, to be at the 8-carbon atom (*32*). If this is correct, the β-derivatives are of the pseudocodeine or allopseudocodeine type, and may be expected to show, in comparison with the α-series, a pharmacological action more closely resembling that of the γ-isomorphine or pseudocodeine derivatives.



XV. α-Chloromorphide.



XVI. β-Chloromorphide (?).

Bromomorphide and bromocodide cannot be caused to undergo rearrangement, and on this account, as well as because of their be-

havior in reactions involving replacement of the halogen, are thought to be of the same structural type as the β-chloro series (*33*, *34*, *35*).

Chlorodihydro-morphide and -codide are most easily obtained by chlorination of dihydromorphine and dihydrocodeine. The halogen atom is certainly at the 6-position, but because of the possibility, or probability, of a Walden inversion during the chlorination, its configuration relative to that of the chlorine in α-chlorocodide is not known. By controlled hydrogenation of β-chlorocodide, a β-chlorodihydrocodide has recently been obtained; its physiological action is not yet known.

Chlorination of dihydroisocodeine does not succeed, and the dihydropseudocodeine and dihydroallopseudocodeine isomers both yield the same 8-chlorodihydrocodide, which is different from any of those so far mentioned (*31*). The nature of the isomerism is still under investigation.

TABLE 6.—*Substitution of the phenolic hydroxyl of the halogeno-morphides*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
86. α-Chloromorphide	36/285	18/127	0.89/10.1	2.68/10.1	0.89/13.6	0.89+/10.1+	0.042/1.2
4. α-Chlorocodide							
142. β-Chloromorphide	207/340	[a]/204	3.34/27.1	4.68/10.1	6.69/16.9	4.68+/6.79+	
5. β-Chlorocodide							
63. Chlorodihydromorphide	27/90	18/54	0.30/3.59	0.13/0.89	0.10/0.89	[b]/4.45+	0.012/0.08
21. Chlorodihydrocodide							
125. Bromomorphide	303/800	303/800	8.65/40.0	6.05/20.0	7.78/[d]	1.73+/15.0+	[c]/[e]
124. Bromocodide							

[a] More convulsant in rabbits than in mice. In the former the minimal convulsant dose was 134 mg per kg, 90 percent of the A. F. D.; in the latter it was 207 mg per kg.
[b] None with doses of 0.1 to 1.0 mg per kg.
[c] 3.0 mg per kg decreased the respiratory rate
[d] None up to 30.0 mg per kg.
[e] No respiratory effect observed with 10 or 20 mg per kg.

Among the halogeno derivatives summarized in table 6, the codides were less toxic than the morphides, but in spite of this, the incidence of convulsions in relation to fatal dose was greater with the codides. In other respects the usual picture of decreased activity when the phenolic hydroxyl is covered was apparent.

To sum up the comparisons of section I (tables 1 to 6) toxicity is not uniformly affected but is usually increased, convulsant action is almost always increased, and all other effects are almost always decreased by muzzling the phenolic hydroxyl and the result is essentially the same regardless of the way in which other portions of the morphine molecule are modified.

2. The Alcoholic Hydroxyl Group

(a) CHANGES IN POSITION OR CONFIGURATION

The secondary alcoholic hydroxyl group present in the naturally occurring drugs, morphine and codeine, is a point of exceptional

interest in the molecule because of the numerous transformations that it may undergo, and the profound change that is produced in physiological activity by even small changes. As has been mentioned above, three isomers of morphine and of codeine are known, differing from the parent alkaloids in the configuration and in the position of the hydroxyl group. Whereas α-isomorphine and isocodeine can be compared directly with morphine and codeine, respectively, for the physiological effect of changing the configuration of the alcoholic hydroxyl, in β- and γ-isomorphines, and in allopseudo- and pseudocodeines, the factor of a new position of the double bond is introduced in addition to the shift of the hydroxyl group to the 8-position in two configurations. In the dihydro series the possible disturbing effect of this change in the position of the alicyclic double linkage no longer is present. A comparison of the effect of position and configuration analogous to that for the hydroxyl can also be made in the extensive series of alcoholic methyl and ethyl ethers of the morphine and codeine isomers and their dihydro derivatives that were prepared for this study (*8*). These alcoholic ethers, compared among themselves, yield additional information on the effect of configurational and positional isomerism, and, compared with the unalkylated hydroxy compounds, demonstrate the striking effect of covering the alcoholic hydroxyl. A similar effect, though less marked, is seen in a comparison of the morphine or codeine series with the monoacetylmorphines and acetylcodeines and their dihydro derivatives.

TABLE 7.—*Changes in configuration of the alcoholic hydroxyl (6-carbon) (2)*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine	531/890	531/(a)	6.75/22.2	0.75/0.80	0.57/0.89	0.22/0.13	0.15/0.15
236. α-Isomorphine							
37. Dihydromorphine	133/890	(b)/(c)	17.7/22.2	0.26/0.80	1.77/0.80	0.17/0.18	0.11/0.13
*265. Dihydro-α-isomorphine							
2. Codeine	241/589	161/589	36.1/58.9	8.04/13.0	8.04/13.0	16.0+/(d)	1.3/1.5
36. Isocodeine							
20. Dihydrocodeine	225/296	168/(e)	14.1/29.8	7.20/1.91	6.45/0.98	3.22+/0.98+	0.9/0.22
51. Dihydroisocodeine							
111. Heterocodeine	72/130	65/90	1.40/0.70	0.48/1.25	0.32/0.50	2.40+/0.5+	0.016/0.01
*302. α-Isomorphine alcoholic methyl ether.							
*112. Dihydroheterocodeine	71/245	71/245	1.70/0.36	0.17/0.06	0.17/0.05	0.17/0.06	----------
*315. Dihydro-α-isomorphine alcoholic methyl ether.**							----------
*296. Morphine alcoholic ethyl ether	109/94	70/66	0.54/0.47	0.31/0.25	0.23/0.17	0.23+/1.70+	----------
*313. α-Isomorphine alcoholic ethyl ether.**							----------
*297. Dihydromorphine alcoholic ethyl ether	93/54	70/41	0.47/0.27	0.23/0.08	0.15/0.07	0.15+/0.08+	----------
*314. Dihydro-α-isomorphine alcoholic ethyl ether.**							----------

* Convulsions do not always occur with fatal doses.
b Convulsions infrequent with fatal doses.
c Convulsions rarely occur with fatal doses, never with recovery.
d None with 6 to 16 mg per kg.
e With fatal doses, twitching of muscles, slight increase in reflexes, but no convulsions.

TABLE 8.—*Changes in configuration of the alcoholic hydroxyl (8-carbon) (36)*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
140. β-Isomorphine	324/2000+	324/(a)	74.0/133+	10.1/7.09	9.26/7.09	4.63/1.77	2.14/2.36
141. γ-Isomorphine							
*266. Dihydro-β-isomorphine	152/1687	152/(a)	22.2/133+	3.11/4.44	4.45/8.87	0.89+/2.66	0.26/1.45
*158. Dihydro-γ-isomorphine							
64. Allopseudocodeine	267/1780	178/(a)	80.1/89.1	13.3/17.8	26.7/22.2	13.3+/4.45	(b)/48.0
3. Pseudocodeine							
*165. Dihydroallopseudocodeine	392/975	325/(a)	74.1/110.2	7.09/4.24	7.09/16.9	9.27+/3.39	2.0/49.0
*99. Dihydropseudocodeine							

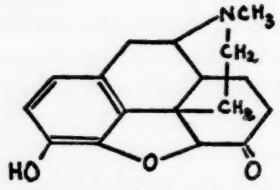
* Neither increase in reflexes nor convulsions have been seen.
b Up to 30 mg per kg there is no significant effect on respiratory rate or tidal volume.

Tables 7 and 8 each include four pairs of compounds in which the sole change is in the configuration of the alcoholic hydroxyl group. The data for these pairs show the most consistent changes in pharmacological results. The shift always reduced toxicity and the convulsant action of toxic doses; it also decreased depressant action in the rat. The other effects were less uniformly modified. Table 7 also includes four pairs of compounds in which a *muzzled* hydroxyl undergoes the same configurational shift, for which the results were not uniform. In cats, the trend was toward greater activity in the α-type of compound as compared with its diastereomer, and in the γ-type as compared with its diastereomer. The effect of the diastereomers on respiration often was not significantly different, and in some instances was less in α- or γ-compounds. The intestinal activity of the dog was less affected by codeine or allopseudocodeine than by isocodeine or pseudocodeine, respectively. On the other hand, the circulatory effect in both the dog and the cat was less with the α- and γ-isomers, that is, the iso- and pseudo-series configuration (*21*, *37*).

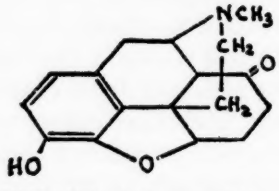
Clinical studies which have been carried out with the most promising of the isomers and their dihydro derivatives will be described in the third paper of this series.

There is at present no way to demonstrate the configuration of the alcoholic hydroxyl in any of the isomers, nor does their chemical behavior give any hint as to which of the 6-hydroxy derivatives is spatially similar to which of the 8-hydroxy compounds. Pharmacological similarities, however, quantitative as well as qualitative, indicate strongly that the spatial position of the hydroxyl (or ether group) relative to the plane of the nitrogen-containing ring is the same in the first member of each pair in table 7 as in the first member of each pair in table 8. That is, morphine and codeine show many pharmacological resemblances to β-isomorphine and allopseudocodeine, while α-isomorphine and isocodeine resemble γ-isomorphine and pseudocodeine, respectively.

Although a comparison of diastereomers, as morphine with α-isomorphine, or β- with γ-isomorphine, gives an idea of the pharmacological result of configurational changes at C-6 or C-8, no conclusion can be drawn in this series from a comparison of 6-hydroxy and 8-hydroxy derivatives, for the pharmacological picture is a resultant of a double change, positional and spatial. In order to determine the relative effectiveness of groups at C-6 and C-8, the asymmetry at these points must be destroyed. This condition is fulfilled in the morphine ketone types. While codeinone and pseudocodeinone, the oxidation products of the codeine-isocodeine and the pseudocodeine-allopseudocodeine pairs, respectively, have long been known, the former is such a strong skin irritant (*38*) that its study was not undertaken. The pair introduce, moreover, the complication of the change in position of the double linkage. In the dihydroketone series these



XVII. Dihydromorphinone.



XVIII. Dihydroisomorphinone.

objections are eliminated. Dihydromorphinone, the keto analog of dihydromorphine and dihydro-α-isomorphine, is prepared by catalytic rearrangement of morphine (*39*), dihydrocodeinone by a similar rearrangement of codeine (*40*), or by hydrolysis of dihydrothebaine, the methyl enolate of dihydrocodeinone (*41*). The 8-keto series must be prepared from pseudocodeinone (from oxidation of pseudocodeine) by hydrogenation under such conditions that the ether bridge remains undisturbed. The resulting dihydropseudocodeinone, in contrast to dihydrocodeinone, can be demethylated smoothly to the phenolic analog (15).

TABLE 9.—*Shift of effective group from C-6 to C-8 with elimination of spatial isomerism* (*42*)

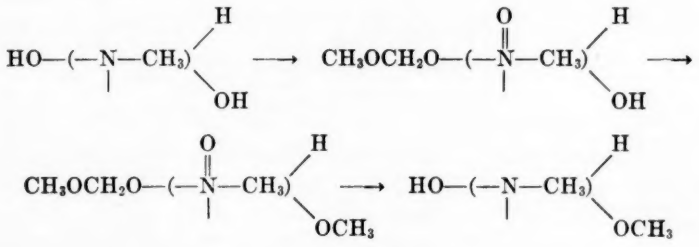
	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
123. Dihydromorphinone	84/210	67/210	0.88/3.50	0.17/2.00	0.17/1.00	0.08/2.50	0.011/(a)
*267. Dihydroisomorphinone**							
154. Dihydrocodeinone	86/169	47/169	4.2/16.9	1.28/8.47	0.86/8.47	2.56+/8.47	0.08/(b)
*242. Dihydropseudocodeinone**							

* Less than 1.0 mg per kg.
b Probably more than 10.0 mg per kg.

Both of the 8-keto derivatives (table 9) were much less effective than the 6-keto isomers, which, other variations in the molecule being eliminated, is definite confirmation of the same difference in kind that may be derived from a comparison of tables 7 and 8. One concludes that positional isomerism has a more profound effect on the pharmacological activity of morphine derivatives than has configurational isomerism. (Cf. previous discussions of this question (*18*, *37*).)

(b) MUZZLING THE ALCOHOLIC HYDROXYL

The alkylation of the alcoholic hydroxyl group in such sensitive substances as the members of the morphine group necessitates prolonged treatment in alkaline solution with alkyl halides or sulfates. Unless phenolic and basic nitrogen groups are protected, their alkylation is inevitable. This difficulty was solved by C. Mannich (*25*), through the device of covering the phenolic hydroxyl with a methoxymethyl group (a benzyl group can also be used), and converting the tertiary nitrogen atom to the oxide. At the end of the alkylation, treatment of the product with sulfurous acid, or with hydrochloric acid and a mild reducing agent, suffices to regenerate the phenolic group and the tertiary nitrogen. (See also reference (*43*).) In outline, the procedure is as follows:



By this method, a number of hitherto unknown alcoholic ethers of morphine have been prepared, for the study of the effect of covering the alcoholic hydroxyl, and the influence of the covering group upon the resultant phenomena (*8*). It should be noted that the alkyl ethers are hydrolyzed (*in vitro* at least) with extreme difficulty, in comparison with those derivatives shown in table 12, in which the covering group is acetyl.

TABLE 10.—*Methyl substitution of the alcoholic hydroxyl*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine	531/72	531/65	6.75/1.40	0.75/0.48	0.57/0.32	0.22/2.40+	0.15/0.016
111. Heterocodeine							
37. Dihydromorphine	133/71	(a)/71	17.7/1.70	0.26/0.17	1.77/0.17	0.17/0.17+	0.11/0.019
*112. Dihydroheterocodeine							
236. α-Isomorphine	890/130	(b)/90	22.2/0.70	0.80/1.25	0.89/8.50	0.13/0.50+	0.15/0.01
*302. α-Isomorphine alcoholic methyl ether.							
*265. Dihydro-α-isomorphine	890/245	(c)/245	22.2/0.36	0.80/0.06	0.80/0.05	0.18/0.06	----------
*315. Dihydro-α-isomorphine alcoholic methyl ether**.							----------
141. γ-Isomorphine	2000+/624	(d)/624	133+/16.9	7.09/3.12	7.09/2.89	1.77/2.89+	2.36/0.19
*303. γ-Isomorphine alcoholic methyl ether**.							
2. Codeine	241/160	161/141	36.1/12.0	8.04/6.00	8.04/6.00	16.0+/9.00+	1.3/0.5
85. Codeine methyl ether							
20. Dihydrocodeine	225/117	168/105	14.1/12.4	7.20/1.16	6.45/1.16	3.22+/7.76+	0.9/0.2
87. Dihydrocodeine methyl ether							
3. Pseudocodeine	1780/459	(d)/321	89.1/75.0	17.8/8.34	22.2/16.6	4.45/8.34+	48.0/4.42
91. Pseudocodeine methyl ether							

* Convulsions infrequent with fatal doses.
b Convulsions do not always occur with fatal doses.
c Convulsions rarely occur with fatal doses, never with recovery.
d Neither increase in reflexes nor convulsions have been seen.

TABLE 11.—*Ethyl and phenyl substitution of the alcoholic hydroxyl*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine	531/109	531/70	6.75/0.54	0.75/0.31	0.57/0.23	0.22/0.23+	0.15/0.011
*296. Morphine alcoholic ethyl ether.							
37. Dihydromorphine	133/93	(a)/70	17.7/0.47	0.26/0.23	1.77/0.15	0.17/0.15+	0.11/0.011
*297. Dihydromorphine alcoholic ethyl ether.							
236. α-Isomorphine	890/94	(b)/66	22.2/0.47	0.80/0.25	0.89/0.17	0.13/1.75+	----------
*313. α-Isomorphine alcoholic ethyl ether**.							----------
*265. Dihydro-α-isomorphine	890/54	(c)/41	22.2/0.27	0.80/0.08	0.80/0.07	0.18/0.08+	----------
*314. Dihydro-α-isomorphine alcoholic ethyl ether**.							----------
141. γ-Isomorphine	2000+/1000	(d)/(e)	133+/100+	7.09/14.6	7.09/(f)	1.77/4.10	----------
*304. γ-Isomorphine alcoholic ethyl ether**.							----------
3. Pseudocodeine	1780/700+	(d)/(d)	----------	----------	----------	----------	----------
246. Pseudocodeine phenyl ether**			----------	----------	----------	----------	----------

* Convulsions infrequent with fatal doses.
b Convulsions do not always occur with fatal doses.
c Convulsions rarely occur with fatal doses, never with recovery.
d Neither increase in reflexes nor convulsions have been seen.
e Muscular twitching, slight increase in reflexes but no convulsions.
f None up to 18.0 mg per kg.

TABLE 12.—*Acetyl substitution of the alcoholic hydroxyl*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine	531/293	531/180	6.75/0.90	0.75/0.18	0.57/0.18	0.22/0.18+	0.15/0.019
199. Monoacetylmorphine							
37. Dihydromorphine	133/99	[a]/89	17.7/11.7	0.26/1.35	1.77/1.35	0.17/0.90	0.11/0.072
*129. Monoacetyldihydromorphine							
236. α-Isomorphine	890/144	[b]/89	22.2/1.35	0.80/0.18	0.89/0.09	0.13/[c]	---/---
*375. Monoacetyl-α-isomorphine**							
140. β-Isomorphine	324/338	324/270	74.0/120+	10.1/22.5	9.26/27.5	4.63/9.00	---/---
*376. Monoacetyl-β-isomorphine**							
141. γ-Isomorphine	2000+/428	[d]/342	133+/22.5	7.09/2.70	7.09/1.80	1.77/4.50+	---/---
*377. Monoacetyl-γ-isomorphine**							
2. Codeine	241/99	161/60	36.1/18.0	8.04/9.03	8.04/7.22	16.0+/4.51+	---/---
366. Acetylcodeine**							
20. Dihydrocodeine	225/91	168/91	14.1/27.1	7.20/4.52	6.45/9.04	3.22+/3.63+	---/---
367. Acetyldihydrocodeine**							
36. Isocodeine	589/112	589/67	58.9/8.92	13.0/3.72	13.0/2.23	[e]/[f]	---/---
*318. Acetylisocodeine**							
51. Dihydroisocodeine	896/114	[g]/67	29.8/6.72	1.91/1.34	0.98+/1.00	0.98+/2.0+	---/---
390. Acetyldihydroisocodeine**							
64. Allopseudocodeine	267/429	178/322	80.1/120+	13.3/50.0+	26.7/[h]	13.3+/27.0	---/---
368. Acetylallopseudocodeine**							
*165. Dihydroallopseudocodeine	392/543	325/543	74.1/120+	7.09/36.2	7.09/[i]	9.27+/27.0	---/---
*369. Acetyldihydroallopseudocodeine**.							
3. Pseudocodeine	1780/750	[d]/413	89.1/70.0	17.8/10.0	22.2/[j]	4.45/8.0+	---/---
389. Acetylpseudocodeine**							
*99. Dihydropseudocodeine	975/850	[d]/638	110.2/60.0	4.24/8.00	16.9/7.00	3.39/5.00	---/---
*319. Acetyldihydropseudocodeine**							

[a] Convulsions infrequent with fatal doses.
[b] Convulsions do not always occur with fatal doses.
[c] Brief nausea in only 3 of 45 animals with doses of 0.05 to 1.0 mg per kg—once with 0.1, once with 0.5, and once with 1.0 mg.
[d] Neither increase in reflexes nor convulsions have been seen.
[e] None with 6 to 16 mg per kg.
[f] Brief nausea in only 2 of 35 animals with doses of 0.5 to 5.0 mg per kg—once with 4.0, and once with 5.0 mg.
[g] With fatal doses twitching of muscles, slight increase in reflexes but no convulsions.
[h] No apparent exciting effect up to 50.0 mg per kg.
[i] None up to 40.0 mg per kg.
[j] None up to 15.0 mg per kg.

A study of tables 10 and 11 shows that muzzling the alcoholic hydroxyl with a methyl or ethyl group, like muzzling of the phenolic hydroxyl, increased toxicity and convulsant action and usually decreased emetic effect. But, unlike muzzling of the phenolic hydroxyl, depressant, analgesic, and exciting effects were increased also, sometimes very markedly. The data in regard to respiratory effect are incomplete but the figures available indicate an increase in effectiveness here also, or no difference, in the muzzled compound.

If an acetyl group was used to cover the alcoholic hydroxyl (table 12) the effect was less regular but the usual picture was, again, increased toxicity and convulsant action, and often increased activity in other respects. It is possible that the irregularity in the activity of the acetylated compounds may be in part explained by the greater

ease with which the acetyl group is removed as compared with methyl or ethyl, so that in the body the substance may have been acting partly as the parent substance with free hydroxyl.

(c) REPLACEMENT OF THE SECONDARY ALCOHOLIC GROUP BY KETONIC OXYGEN

Dihydromorphinone and dihydrocodeinone differ structurally from the pairs dihydromorphine-dihydro-α-isomorphine and dihydrocodeine-dihydroisocodeine, respectively, only in carrying a ketone group at C-6 in place of the secondary alcoholic group, and a similar relationship exists between dihydroisomorphinone and dihydropseudocodeinone and the pairs dihydro-β-isomorphine-dihydro-γ-isomorphine and dihydroallopseudocodeine-dihydropseudocodeine.

In the nuclear alkylated morphine series, which will be discussed in more detail in a later paragraph, one more set of ketones is available for comparison with the alcohols, and shows in even more marked degree the physiological effect of the change.

TABLE 13.—*Keto substitution of the alcoholic hydroxyl*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
37. Dihydromorphine	133/84	[a]/67	17.7/0.88	0.26/0.17	1.77/0.17	0.17/0.08	0.11/0.011
123. Dihydromorphinone							
*265. Dihydro-α-isomorphine	890/84	[b]/67	22.2/0.88	0.80/0.17	0.80/0.17	0.18/0.08	0.13/0.011
123. Dihydromorphinone							
*266. Dihydro-β-isomorphine	152/210	152/210	22.2/3.50	3.11/2.00	4.45/1.00	0.89+/2.50	0.26/[c]
*267. Dihydroisomorphinone**							
*158. Dihydro-γ-isomorphine	1687/210	[d]/210	133+/3.50	4.44/2.00	8.87/1.00	2.66/2.50	1.45/[c]
*267. Dihydroisomorphinone**							
20. Dihydrocodeine	225/86	168/47	14.1/4.20	7.20/1.28	6.45/0.86	3.22+/2.56+	0.9/0.08
154. Dihydrocodeinone							
51. Dihydroisocodeine	896/86	[e]/47	29.8/4.20	1.91/1.28	0.98/0.86	0.98+/2.56+	0.22/0.08
154. Dihydrocodeinone							
*165. Dihydroallopseudocodeine	392/169	325/169	74.1/16.9	7.09/8.47	7.09/8.47	9.27+/8.47	2.0/[f]
*242. Dihydropseudocodeinone**							
*99. Dihydropseudocodeine	975/169	[d]/169	110.2/16.9	4.24/8.47	16.9/8.47	3.39/8.47	49.0/[f]
*242. Dihydropseudocodeinone**							
*399. Methyldihydromorphine**	491/25	[e]/25	70.0/3.0	3.56/0.07	8.91/0.10	0.89/0.07	0.2/0.011
*359. Methyldihydromorphinone**							
*358. Methyldihydrocodeine**	896/55	[d]/50	---/---	25.8/1.00	[h]/2.00	8.96/0.80	[i]/0.3
*357. Methyldihydrocodeinone**							

* Convulsions infrequent with fatal doses.
[b] Convulsions rarely occur with fatal doses, never with recovery.
[c] Less than 1.0 mg per kg.
[d] Neither increase in reflexes nor convulsion have been seen.
[e] With fatal doses twitching of muscle, slight increase in reflexes but no convulsions.
[f] Probably more than 10.0 mg per kg.
[g] No apparent convulsant action.
[h] None up to 30.0 mg per kg.
[i] None up to 10.0 mg per kg.

(d) REPLACEMENT OF THE ALCOHOLIC HYDROXYL BY HYDROGEN

In further pursuance of the physiological significance of the alcoholic hydroxyl, the result of replacement by hydrogen has been studied. For comparison with morphine and codeine themselves, no unhydrogenated desoxy derivatives are known. In desoxymorphine-C (formula XII) and its methyl ether, desoxycodeine-C, we have two compounds that represent β- or γ-isomorphine and allopseudocodeine or pseudocodeine, respectively, in which hydrogen has been substituted for the alcoholic hydroxyl.

In the dihydrogenated series the difficulty concerning the double linkage disappears, and dihydrodesoxymorphine-D (formula XIII) and its methyl ether, dihydrodesoxycodeine-D, are comparable with all the hydroxy analogs, the four dihydrogenated isomeric morphines and codeines respectively.

Two additional comparisons of action between similarly related compounds in the tetrahydro series may be made, namely tetrahydro-γ-isomorphine and tetrahydropseudocodeine (formula VI, R=H, R=CH_3), in which the ether oxygen ring has been opened, with the analogous types, tetrahydrodesoxymorphine (XIV) and its methyl ether, tetrahydrodesoxycodeine (table 14).

(e) REPLACEMENT OF THE ALCOHOLIC HYDROXYL BY HALOGEN

The substitution of halogen for the alcoholic hydroxyl group yields a series of compounds of considerable interest from the standpoint of physiological action. It is unfortunate that the location of the halogen atom (at C–6) is known with certainty (see page 12) only in the derivatives of the α-series, that is α-chloromorphide, α-chlorocodide, and their dihydro derivatives, and even in this series there seems to be no way to determine whether the halogen has the codeine or the isocodeine configuration.

(f) REPLACEMENT OF THE ALCOHOLIC HYDROXYL BY BASIC GROUPS

Replacement of the alcoholic hydroxyl group by radicals of a basic nature is of interest chiefly because it constitutes the most notable exception to the general rule that covering or replacing the hydroxyl results in a drug of increased activity. It should be noted that the introduction of basic groups at other points in the molecule (2-(?) aminomorphine) likewise resulted in a great diminution of physiological effects. The aminomorphides and aminocodides are formed when the halogenomorphides or halogenocodides are treated with amines. As in hydrolysis or alcoholysis, substitution of halogen by basic groups may involve an α, γ-shift, or Walden inversion, or both transformations. From α-chloromorphide or α-chlorocodide, substituted

amino derivatives belonging to the 8-series are obtained exclusively (configuration unknown). From the β-chloro series, or the bromo series, substituted 6-amino derivatives alone are formed (*17*). The substitution products derived from ammonia have only recently been prepared (*26*), and have not been studied pharmacologically.

TABLE 14.—*Replacement of the alcoholic hydroxyl by hydrogen*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
140. β-Isomorphine	324/79	324/79	74.0/0.52	10.1/0.45	9.26/0.45	4.63/0.90+	2.14/0.016
*68. Desoxymorphine-C							
141. γ-Isomorphine	2000+/79	[a]/79	133+/0.52	7.09/0.45	7.09/0.45	1.77/0.90+	2.36/0.016
*68. Desoxymorphine-C							
64. Allopseudocodeine	267/110	178/[c]	80.1/6.00	13.3/1.00	26.7/1.00	13.3+/5.00+	[b]/0.09
67. Desoxycodeine-C							
3. Pseudocodeine	1780/110	[a]/[c]	89.1/6.00	17.8/1.00	22.2/1.00	4.45/5.00+	48.0/0.09
67. Desoxycodeine-C							
37. Dihydromorphine	133/104	[d]/104	17.7/0.32	0.26/0.08	1.77/0.16	0.17/[e]	0.11/0.012
*126. Dihydrodesoxymorphine-D							
*265. Dihydro-α-isomorphine	890/104	[f]/104	22.2/0.32	0.80/0.08	0.80/0.16	0.18/[e]	0.13/0.012
*126. Dihydrodesoxymorphine-D							
*266. Dihydro-β-isomorphine	152/104	152/104	22.2/0.32	3.11/0.08	4.45/0.16	0.89+/[e]	0.26/0.012
*126. Dihydrodesoxymorphine-D							
*158. Dihydro-γ-isomorphine	1687/104	[a]/104	133+/0.32	4.44/0.08	8.87/0.16	2.66/[e]	1.45/0.012
*126. Dihydrodesoxymorphine-D							
20. Dihydrocodeine	225/131	168/65	14.1/2.12	7.20/1.96	6.45/1.96	3.22+/0.65+	0.9/0.08
16. Dihydrodesoxycodeine-D							
51. Dihydroisocodeine	896/131	[g]/65	29.8/2.12	1.91/1.96	0.98/1.96	0.98+/0.65+	0.22/0.08
16. Dihydrodesoxycodeine-D							
*165. Dihydroallopseudocodeine	392/131	325/65	74.1/2.12	7.09/1.96	7.09/1.96	9.27+/0.65+	2.0/0.08
16. Dihydrodesoxycodeine-D							
*99. Dihydropseudocodeine	975/131	[a]/65	110.2/2.12	4.24/1.96	16.9/1.96	3.39/0.65+	49.0/0.08
16. Dihydrodesoxycodeine-D							
*308. Tetrahydro-γ-isomorphine	267/221	[a]/[h]	80+/14.08	8.90/0.62	17.8/1.86	1.78/6.20+	----------
*55. Tetrahydrodesoxymorphine							
169. Tetrahydroallopseudocodeine	425/133	[a]/133	----------	----------	----------	----------	----------
54. Tetrahydrodesoxycodeine							
69. Tetrahydropseudocodeine	417/133	[a]/133	100+/85.48	26.7/4.43	[i]/6.67	17.8/2.21+	[j]/[k]
54. Tetrahydrodesoxycodeine							

[a] Neither increase in reflexes nor convulsions have been seen.
[b] Up to 30.0 mg per kg there is no significant effect on respiratory rate or tidal volume.
[c] Reflexes are exaggerated and convulsions occur in all animals with fatal doses.
[d] Convulsions infrequent with fatal doses.
[e] No emetic effect up to 1.0 mg per kg.
[f] Convulsions rarely occur with fatal doses, never with recovery.
[g] With fatal doses twitching of muscles, slight increase in reflexes but no convulsions.
[h] Brief convulsive movements on stimulation with fatal doses.
[i] None up to 30.0 mg per kg.
[j] No effect on respiratory rate up to 75.0 mg per kg.
[k] Effective dose probably not less than 10.0 mg per kg.

TABLE 15.—*Replacement of the alcoholic hydroxyl by halogen*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine 86. α-Chloromorphide	531/36	531/18	6.75/0.89	0.75/2.68	0.57/0.89	0.22/0.89+	0.15/0.042
236. α-Isomorphine 86. α-Chloromorphide	890/36	(a)/18	22.2/0.89	0.80/2.68	0.89/0.89	0.13/0.89+	0.15/0.042
140. β-Isomorphine 142. β-Chloromorphide	324/207	324/(b)	74.0/3.34	10.1/4.68	9.26/6.69	4.63/4.68+	---/---
141. γ-Isomorphine 142. β-Chloromorphide	2000+/207	(c)/(b)	133+/3.34	7.09/4.68	7.09/6.69	1.77/4.68+	---/---
37. Dihydromorphine 63. Chlorodihydromorphide	133/27	(d)/18	17.7/0.30	0.26/0.13	1.77/0.10	0.17/(e)	0.11/0.012
*265. Dihydro-α-isomorphine 63. Chlorodihydromorphide	890/27	(f)/18	22.2/0.30	0.80/0.13	0.80/0.10	0.18/(e)	0.13/0.012
2. Codeine 4. α-Chlorocodide	241/285	161/127	36.1/10.1	8.04/10.1	8.04/13.6	16.0+/10.1	1.3/1.2
36. Isocodeine 4. α-Chlorocodide	589/285	589/127	58.9/10.1	13.0/10.1	13.0/13.6	(g)/10.1	1.5/1.2
64. Allopseudocodeine 5. β-Chlorocodide	267/340	178/204	80.1/27.1	13.3/10.1	26.7/16.9	13.3+/6.79+	(h)/(i)
3. Pseudocodeine 5. β-Chlorocodide	1780/340	(j)/204	89.1/27.1	17.8/10.1	22.2/16.9	4.45/6.79+	48.0/(i)
20. Dihydrocodeine 21. Chlorodihydrocodide	225/90	168/54	14.1/3.59	7.20/0.89	6.45/0.89	3.22+/4.45+	0.9/0.08
51. Dihydroisocodeine 21. Chlorodihydrocodide	896/90	(k)/54	29.8/3.59	1.91/0.89	0.98/0.89	0.98+/4.45+	0.22/0.08
1. Morphine 125. Bromomorphide**	531/303	531/303	6.75/8.65	0.75/6.05	0.57/7.78	0.22/1.73+	0.15/(l)
2. Codeine 124. Bromocodide**	241/800	161/800	36.1/40.0	8.04/20.0	8.04/(l)	16.0+/15.0+	1.3/(m)

[a] Convulsions do not always occur with fatal doses.
[b] Convulsive movements with fatal doses in mice; convulsions with 90 percent of fatal dose (134 mg per kg) in rabbits.
[c] Neither increase in reflexes nor convulsions have been seen.
[d] Convulsions infrequent with fatal doses.
[e] None with doses of 0.1 to 1.0 mg per kg.
[f] Convulsions rarely occur with fatal doses, never with recovery.
[g] None with 6 to 16 mg per kg.
[h] Up to 30 mg per kg there is no significant effect on respiratory rate or tidal volume.
[i] Like allopseudocodeine, no depressant effect on respiratory activity.
[j] With fatal doses twitching of muscles, slight increase in reflexes but no convulsions.
[k] 3.0 mg per kg decreased the respiratory rate.
[l] None up to 30.0 mg per kg.
[m] No respiratory effect observed with 10 or 20 mg per kg.

TABLE 16.—*Replacement of the alcoholic hydroxyl by basic groups*

	Toxicity	Convulsant action	Analgesia	Exciting effect	Emetic action
1. Morphine *360. 6-Piperidomorphide**	531/550	531/550	0.75/9.00	0.57/8.00	0.22/8.00
37. Dihydromorphine *361. 6-Piperidodihydromorphide**	133/275	(a)/(b)	0.26/25.0	1.77/50.0	0.17/5.0
140. β-Isomorphine *363. 8-Piperidomorphide**	324/1000	324/(b)	10.1/30.0	9.26/(c)	4.63/25.0
140. β-Isomorphine 364. 8-Diethylaminomorphide**	324/500	324/400	10.1/10.0	9.26/(c)	4.63/10.0
64. Allopseudocodeine 362. 8-Piperidocodide**	267/551	178/551	13.3/50+	26.7/(d)	13.3+/40.0
64. Allopseudocodeine 365. 8-Diethylaminocodide**	267/325	178/292	13.3/25.0	26.7/(c)	13.3+/20.0

[a] Convulsions infrequent with fatal doses.
[b] No increase in reflexes or convulsions.
[c] Not typically exciting (see text).
[d] None up to 50.0 mg per kg.

With one exception, replacement of the secondary alcoholic group by ketonic oxygen (table 13) increased toxicity; also the keto derivatives were the more convulsant. Other effects, except emetic action, were almost always increased. But, although the intensity of action was notably increased, it is important to note that the duration of effect was decreased (an outstanding exception will be discussed later), and it has been demonstrated clinically that the addiction property is still present (No. 123, Dilaudid, and No. 154, Dicodid) to an undesirable degree (*44*).

Substitution of hydrogen for the alcoholic hydroxyl (table 14) had the most marked and most consistent effect upon pharmacological action of any of the chemical changes described so far. Toxicity was definitely and often markedly increased; convulsant action was usually increased. Depressant, excitant, analgesic, and respiratory effects were very markedly increased, while the emetic effect of the hydrogen substituted compounds was irregular. As with the keto derivatives, coincident with the increased activity of the members of the group, the duration of action was decreased. The action of the most promising compound of the series, dihydrodesoxymorphine-D, has been studied in several clinics (*45*, *46*) and will be considered in detail in the third paper of this series.

Replacement of the alcoholic hydroxyl by halogen (table 15) almost always increased toxicity and convulsant action. Bromocodide was a striking exception, since it was much less convulsant than codeine. This suggests the possibility that we were dealing with a bromo derivative of the pseudocodeine (or isocodeine) type. The other effects of the halogen derivatives were usually increased but there were exceptions for which no explanation can be offered at the present time. It is perhaps significant that the analgesic and exciting effects of α-chloromorphide, of α-chlorocodide, of bromomorphide, and of bromocodide were in each instance less than the corresponding effects of morphine and codeine, respectively.

Not only were toxicity, convulsant action, and other morphine-like effects decreased in the aminomorphides and aminocodides (table 16), but there was a qualitative difference in the picture which these substances produced when administered to cats. Typical morphine-like excitement did not occur, except possibly to a very slight extent with Nos. 360 and 361. Instead, especially with Nos. 363, 364, and 365, there was marked incoordination, trembling that was exaggerated on handling, and convulsive movements or generalized clonic convulsions. The heart rate nevertheless was increased moderately and the pupils were dilated. The incoordination and convulsant action were like those seen with simpler piperidino compounds, piperidino-ethanol and 3-(2-piperidino-1-hydroxy-ethyl) phenanthrene, for example (*47*).

The effect of changes in the alcoholic hydroxyl may be summarized as follows: Most substitutions, ketonic oxygen, hydrogen, halogen, or covering with methyl, ethyl, and acetyl groups, tended to increase

toxicity and convulsant action and to increase other morphine-like effects as well. The most regular in effect was hydrogen substitution, the least regular were acetylation and substitution by halogen. In marked contrast was the decrease in effect, and the qualitative change in the picture, when the alcoholic hydroxyl was replaced by a basic group. It may be inferred from the results obtained with the isomeric dihydroketones, that a shift of the alcoholic hydroxyl group from the 6- to the 8-carbon had a much more profound effect than spatial isomerism upon pharmacological action.

3. The Ether Oxygen Bridge

The five-membered oxygen-containing ring present in the morphine alkaloids forms part of a partially hydrogenated phenanthrylene oxide system, or, as far as the immediately adjacent rings are concerned, of a partially hydrogenated dibenzofuran system. Contrary to the chemical inactivity to be expected of the ether oxygen in a dibenzofuran or tetrahydrodibenzofuran grouping, the ether ring of the morphine group is opened by reductive processes with extreme ease whenever a double linkage is present in the 6, 7-position (i. e. "conjugated" with the ether oxygen), or in certain other examples where halogen or ketonic oxygen is attached to the 6-carbon atom (*48*, *49*). The compounds resulting from this type of reduction have a new phenolic hydroxyl group at the 4-position and necessarily contain two or four more hydrogen atoms than the starting material. Comparisons of the physiological effect of opening the ether ring by addition of hydrogen at oxygen and C-5, without the complication of saturating a double bond, are interesting.

TABLE 17.—*Opening of the ether oxygen bridge*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
*126. Dihydrodesoxymorphine-D	104/221	104/(b)	0.32/14.0	0.08/0.62	0.16/1.86	(a)/6.20+	0.012/(c)
*55. Tetrahydrodesoxymorphine							
16. Dihydrodesoxycodeine-D	131/133	65/133	2.12/35.4	1.96/4.43	1.96/6.67	0.65+/2.21+	0.08/(d)
54. Tetrahydrodesoxycodeine							
*99. Dihydropseudocodeine	975/417	(e)/(e)	110.2/100+	4.24/26.7	16.9/(f)	3.39/17.8	----------
69. Tetrahydropseudocodeine							----------
*165. Dihydroallopseudocodeine	392/425	325/(e)	----------	----------	----------	----------	----------
169. Tetrahydroallopseudocodeine			----------	----------	----------	----------	----------
*158. Dihydro-γ-isomorphine	1687/267	(e)/(e)	133+/80+	4.44/8.90	8.87/17.8	2.66/1.78	----------
*308. Tetrahydro-γ-isomorphine							----------
154. Dihydrocodeinone	86/161	47/124	----------	----------	----------	----------	----------
130. Dihydrothebainone**			----------	----------	----------	----------	----------

[a] No emetic effect up to 1.0 mg per kg.
[b] Brief convulsive movements on stimulation with fatal doses.
[c] Effective dose probably between 1.0 and 2.0 mg per kg.
[d] Effective dose probably not less than 10.0 mg per kg.
[e] Neither increase in reflexes nor convulsions have been seen.
[f] None up to 30.0 mg per kg.

Comparisons in this group, however (table 17), must be made with caution because of the other changes which have been effected in the

morphine molecule to any or all of which the difference may be due. In particular, the rupture of the oxygen-C-5 linkage may have influenced the activity of peripheral functional groups (hydroxyl, ketone) in ring III. Such a possible influence is eliminated in the derivatives of the desoxy series, which carry no groups in this ring. The general trend was in the direction of decreased toxicity and decreased activity in the compound with the ether bridge opened. It is surprising, in view of other results, that the introduction of a new phenolic hydroxyl did not have just the opposite effect, especially that it did not increase emetic action.

4. The Alicyclic Unsaturated Linkages

In discussing the effect of saturation of the alicyclic double linkage in the morphine group, a distinction must be drawn according to the location of the double linkage. In unsaturated members of the series that are of the type of morphine itself, the unsaturation lies in the β, γ-position to the alcoholic hydroxyl group, i. e., these may be regarded as analogs of allyl alcohol. The chemical effect of the double bond upon such substituents as hydroxyl and halogen so located with reference to the double bond is to cause a considerable activation, and it might be predicted that physiological effects due to the hydroxyl group, for example, would be greater in the unsaturated series than in the corresponding hydrogenated derivatives. The alcoholic hydroxyl group, however, as shown above, exerts in general an inhibiting effect, and therefore, in the saturated derivatives, this inhibiting effect should in general be reduced. Similar considerations hold for the double linkage in the 6, 7-position, that is in compounds of the pseudocodeine or γ-isomorphine types. In the 6, 7-unsaturated series, moreover, there is unquestionably a mutual influence between the ether-linked oxygen and the double linkage, as has already been mentioned for reductive processes, and as is further evident in other types of addition reactions (*15*, *34*, *50*). Beyond the influence which the unsaturation may have upon groups in its immediate vicinity, it may be expected that some change in physiological action will be observed as a result of the saturation of the bond itself. Only with desoxymorphine-C and desoxycodeine-C, where ring III carries no substituent, can this effect be dissociated from that due to possible activation of adjacent groups (except the ether oxygen).

Two 6, 7-unsaturated derivatives that may be included in this series differ from the simple unsaturated derivatives in that the unsaturation is one resulting from enolization. Such enol ethers or enol esters undergo hydrolysis with great ease in comparison with their hydrogenated analogs, and a comparison of action must be made with caution, for the activity measured for the unhydrogenated derivative may be actually that of the hydrolysis product.

TABLE 18.—*Saturation of the 7, 8-double bond*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine 37. Dihydromorphine	531/133	531/[a]	6.75/17.7	0.75/0.26	0.57/1.77	0.22/0.17	0.15/0.11
305. Benzylmorphine** *306. Benzyldihydromorphine**	35/35	35/35	[b]/[c]	7.87/2.40	7.87/2.18	8.74/1.74	[e]/[f]
111. Heterocodeine *112. Dihydroheterocodeine	72/71	65/71	1.40/1.70	0.48/0.17	0.32/0.17	2.40+/0.17+	0.016/0.019
*296. Morphine alcoholic ethyl ether *297. Dihydromorphine alcoholic ethyl ether.	109/93	70/70	0.54/0.47	0.31/0.23	0.23/0.15	0.23+/0.15+	0.011/0.011
199. Monoacetylmorphine *129. Monoacetyldihydromorphine	293/99	180/89	0.90/11.7	0.18/1.35	0.18/1.35	0.18+/0.90	0.019/0.072
127. Diacetylmorphine 128. Diacetyldihydromorphine	262/119	196/119	1.10/9.10	0.43/1.82	0.40/0.90	[d]/1.82	0.015/0.125
86. α-Chloromorphide 63. Chlorodihydromorphide	36/27	18/18	0.89/0.30	2.68/0.13	0.89/0.10	0.89+/[e]	0.042/0.012
*360. 6-Piperidomorphide** *361. 6-Piperidodihydromorphide**	550/275	550/[f]	---/---	9.00/25.0	8.00/50.0	8.00/5.0	---/---
49. Pseudomorphine** *65. Tetrahydropseudomorphine**	2000+/700	[f]/[h]	---/---	[g]/40.0+	50.0/[i]	50.0+/40.0+	---/---
236. α-Isomorphine *265. Dihydro-α-isomorphine	890/890	[j]/[k]	22.2/22.2	0.80/0.80	0.89/0.80	0.13/0.18	0.15/0.13
*302. α-Isomorphine alcoholic methyl ether *315. Dihydro-α-isomorphine alcoholic methyl ether.**	130/245	90/245	0.70/0.36	1.25/0.06	0.50/0.05	0.50+/0.06	---/---
*313. α-Isomorphine alcoholic ethyl ether** *314. Dihydro-α-isomorphine alcoholic ethyl ether**.	94/54	66/41	0.47/0.27	0.25/0.08	0.17/0.07	1.70+/0.08+	---/---
2. Codeine 20. Dihydrocodeine	241/225	161/168	36.1/14.1	8.04/7.20	8.04/6.45	16.0+/3.22+	1.3/0.9
85. Codeine methyl ether 87. Dihydrocodeine methyl ether	160/117	141/105	12.0/12.4	6.00/1.16	6.00/1.16	9.00+/7.76+	0.5/0.2
366. Acetylcodeine** 367. Acetyldihydrocodeine**	99/91	60/91	18.0/27.0	9.03/4.52	7.22/9.04	4.51+/3.63+	---/---
36. Isocodeine 51. Dihydroisocodeine	589/896	589/[m]	58.9/29.8	13.0/1.91	13.0/0.98	[l]/0.98+	1.5/0.22
*300. Ethyl-α-isomorphine** *301. Ethyldihydro-α-isomorphine**	750/331	[f]/[p]	[n]/47.3	5.00/2.83	[o]/2.83	2.00/2.36	---/---
318. Acetylisocodeine** 390. Acetyldihydroisocodeine**	112/114	67/67	8.92/6.72	3.72/1.34	2.23/1.00	4.0+/2.0+	---/---
4. α-Chlorocodide 21. Chlorodihydrocodide	285/90	127/54	10.1/3.59	10.1/0.89	13.6/0.89	10.1+/4.45+	1.2/0.08
320. Hydroxycodeinone** 322. Dihydrohydroxycodeinone**	23/426	23/426	30+/1.34	4.68/1.34	[q]/0.89	0.85+/0.89+	[r]/0.10
113. Thebainone** 130. Dihydrothebainone**	94/161	71/124	---/---	---/---	---/---	---/---	---/---

[a] Convulsions infrequent with fatal doses.
[b] Three animals receiving 20 mg per kg had convulsions and two died; smaller doses did not depress the righting reflex.
[c] M. E. D. 21.8; convulsions did not occur nor death until a dose of 35 mg per kg was reached.
[d] None with doses of 0.3 to 2.0 mg per kg.
[e] None with doses of 0.1 to 1.0 mg per kg.
[f] No increase in reflexes or convulsions.
[g] None up to 50.0 mg per kg intramuscularly or 500.0 mg per kg orally.
[h] Convulsions did not occur, but in three instances a late increase in reflexes was seen.
[i] None up to 40.0 mg per kg.
[j] Convulsions do not always occur with fatal doses.
[k] Convulsions rarely occur with fatal doses, never with recovery.
[l] None with 6 to 16 mg per kg.
[m] With fatal doses twitching of muscles, slight increase in reflexes but no convulsions.
[n] Three of ten animals receiving 70.0 mg per kg had convulsions and died, the righting reflex was not depressed by smaller doses.
[o] No trace of exciting effect up to 10.0 mg per kg.
[p] Occasional twitching; rarely hyperirritability during recovery; no convulsions.
[q] No exciting effect with 0.7 to 3.0 mg per kg; convulsions occurred with 5.5, 6.0, and 7.0 mg per kg.
[r] No decrease in respiratory activity with 0.1 to 3.0 mg per kg; reflex activity increased at the higher dose.
[s] Up to 20 mg per kg no significant effect on respiratory rate or minute volume.
[t] With 20 mg per kg minute volume 80 per cent of normal (average of 10 animals); with 40 mg per kg minute volume 110 per cent of normal (reflex activity increased); doses less than 10 mg per kg had no significant effect on respiratory rate or minute volume.

TABLE 19.—*Saturation of the 6, 7-double bond*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
140. β-Isomorphine *266. Dihydro-β-isomorphine	324/152	324/152	74.0/22.2	10.1/3.11	9.26/4.45	4.63/0.89+	2.14/0.26
142. β-Chloromorphide (?) 63. Chlorodihydromorphide	207/27	[a]/18	3.34/0.30	4.68/0.13	6.69/0.10	4.68+/[b]	---/---
141. γ-Isomorphine *158. Dihydro-γ-isomorphine	2000+/1687	[c]/[c]	133+/133+	7.09/4.44	7.09/8.87	1.77/2.66	2.36/1.45
*68. Desoxymorphine-C *126. Dihydrodesoxymorphine-D	79/104	79/104	0.52/0.32	0.45/0.08	0.45/0.16	0.90+/[d]	0.016/0.012
64. Allopseudocodeine *165. Dihydroallopseudocodeine	267/392	178/325	80.1/74.1	13.3/7.09	26.7/7.09	13.3+/9.27+	[e]/2.0
368. Acetylallopseudocodeine** *369. Acetyldihydroallopseudocodeine**.	429/543	322/543	120+/120+	50+/36.2	[f]/[e]	27.0/27.0	---/---
3. Pseudocodeine *99. Dihydropseudocodeine	1780/975	[c]/[c]	89.1/110.2	17.8/4.24	22.2/16.9	4.45/3.39	48.0/49.0
*298. Ethyl-γ-isomorphine** *299. Ethyldihydro-γ-isomorphine**.	1157/1200	[c]/[c]	100+/100+	10.7/5.00	[h]/20.0	1.79/2.00	---/---
389. Acetylpseudocodeine** *319. Acetyldihydropseudocodeine**	750/850	413/638	70.0/60.0	10.0/8.00	[i]/7.00	8.0+/5.00	---/---
67. Desoxycodeine-C 16. Dihydrodesoxycodeine-D	110/131	[j]/65	6.00/2.12	1.00/1.96	1.00/1.96	5.00+/0.65+	0.09/0.08
5. β-Chlorocodide (?) 21. Chlorodihydrocodide	340/90	204/54	27.1/3.59	10.1/0.89	16.9/0.89	6.79+/4.45+	[k]/0.08
371. Dihydrocodeinone enol acetate** 367. Acetyldihydrocodeine**	81/91	65/91	6.32/27.0	1.35/4.52	0.90/9.04	1.12+/3.63+	---/---
97. Dihydrothebaine** 87. Tetrahydrothebaine	96/117	77/105	---	2.61/1.16	2.61/1.16	8.70+/7.76+	0.5/0.2

[a] Convulsive movements with fatal doses in mice; convulsions with 90 percent of the fatal dose (134 mg per kg) in rabbits.
[b] None with doses of 0.1 to 1.0 mg per kg.
[c] Neither increase in reflexes nor convulsions have been seen.
[d] No emetic effect up to 1.0 mg per kg.
[e] Up to 30.0 mg per kg there is no significant effect on respiratory rate or tidal volume.
[f] No apparent exciting effect up to 50.0 mg per kg.
[g] None up to 40.0 mg per kg.
[h] No excitement up to 20.0 mg per kg.
[i] None up to 15.0 mg per kg.
[j] Reflexes are exaggerated and convulsions occur in all animals with fatal doses.
[k] No depressant effect on respiratory activity.

TABLE 20.—*Incidence of variation in effect with hydrogenation*

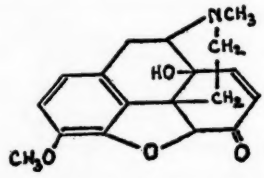
	Effect increased	Effect decreased	Effect unchanged	No data
	Saturation of 7, 8-double bond			
Toxicity	12	4	5	---
Convulsant action	[a] 6(6)	[a] 7(15)	8	---
Depressant effect	8	4	4	5
Analgesia	14	3	2	2
Exciting effect	12	6	1	2
Emetic action	11	3	5	2
Respiratory effect	7	2	3	9
	Saturation of 6, 7-double bond			
Toxicity	[l]	6	2	---
Convulsant action	[a] 4(2)	[a] 6(6)	[a] 3(5)	---
Depressant effect	5	1	[m]	4
Analgesia	10	2	---	1
Exciting effect	8	1	3	1
Emetic action	5	6	1	1
Respiratory effect	5	0	3	5

[a] The first figure is derived from a direct comparison of minimal convulsant doses, the figure in parentheses from a comparison of the relation of the convulsant to the fatal dose.

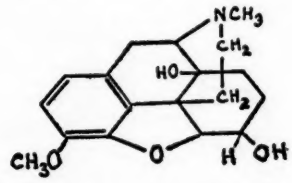
The effect of saturation by hydrogenation either of the 6, 7- or of the 7, 8-double bond (tables 18, 19, and 20) tended toward decreased convulsant action and increased activity in other respects, particularly analgesic effect, but there were so many exceptions that one is forced to conclude that in a specific instance the effect would be unpredictable. The results do not fall into line any better if the grouping is on the basis of the presence of a free alcoholic hydroxyl, the activity of which, as explained above, might be influenced by the removal of the double bond.

5. The Influence of Nuclear Substituents

In considering the result of substitution of new groups into the morphine nucleus, a distinction must be drawn between those derivatives in which the substitution is in the aromatic nucleus, and those in which substitution has been made in the alicyclic portion of the molecule. Only a few compounds of either type are known. By the action of chlorine and bromine, chloro- and bromo-morphine and



XIX. Hydroxycodeinone.



XX. Dihydrohydroxycodeine.

-codeine are obtained, in which the halogen atom occupies the 1-position in the aromatic nucleus (*51*). An aminomorphine is also known, which is prepared by reduction of the nitrosomorphine that results from treatment of morphine with nitrogen oxides. The amino group is believed to be in the 2-position (*52*). The relationship of aminomorphine to aminocodeine (from reduction of nitrocodeine) has not been established. In addition to these aromatic substitution products, there exist the acetocodeine types and the sulfonic acids, whose structure and physiological action will be considered in later papers.

Among the morphine derivatives carrying new substituents in the hydro-aromatic portion of the nucleus, the compounds derived from hydroxycodeinone are most easily accessible. Hydroxycodeinone results from the action of hydrogen peroxide on thebaine (*53*). The reaction is believed to involve a 1, 4-addition of hydrogen peroxide to the system of unsaturated linkages, followed by loss of methanol (*54*). Evidence for the location of the hydroxyl group on C–14 is not very satisfactory.

Hydroxycodeinone is an exceedingly disagreeable skin irritant (*55*), but on hydrogenation of the 7, 8-double bond this property disappears. The product, dihydrohydroxycodeinone, in the form of its salts, is

the narcotic Eukodal (*56*). By reduction of the ketonic group of hydroxycodeinone (metal combinations), 14-hydroxycodeine is obtained. It is not known whether this product is of the codeine or the isocodeine type. 14-Hydroxycodeine gives on catalytic reduction dihydrohydroxycodeine-A, an isomer of the dihydrohydroxycodeines-B and -C which result from reduction of the ketonic group of dihydrohydroxycodeinone with metal combinations (*57*).

The reaction of thebaine with bromine appears to take a course parallel to that with hydrogen peroxide, and results in 14-bromocodeinone (*54*, *58*).

Another type of nuclear substituted morphine derivative has recently been prepared in our laboratories through the application of the Grignard reaction to the enol ethers or enol esters of the dihydroketones of the morphine series. An alkyl group is introduced at C-5 or C-7, through a 1, 2- or 1, 4-addition of the organomagnesium halide, and the oxide ring is opened, with simultaneous hydrolysis at the enol ether or ester group (*59*). The resulting alkylated phenolic

XXI. Probable structures for methyldihydromorphinone.

ketones can be converted back to the true morphine types through closure of the 4, 5-oxide ring by the method of Schöpf (*60*, *61*, *62*).

The position of the alkyl group in the methyldihydrocodeinone and isomethyldihydrocodeinone so obtained is not certain. By demethylation of methyldihydrocodeinone, a nuclear methylated analog of dihydromorphinone is formed, or by reduction of the ketonic oxygen, methylated analogs of dihydrocodeine and dihydromorphine may be obtained. The demethylation of derivatives of the iso series has not yet been accomplished.

TABLE 21.—*Nuclear substitution in the aromatic ring*

	Toxicity	Convulsant action	Analgesia	Exciting effect	Emetic action
1. Morphine 66. Aminomorphine**	531/402	531/(*)	0.75/24.1	0.57/8.04	0.22/20.1
2. Codeine 139. Chlorocodeine**	241/18	161/17	8.04/15.0	8.04/20+	16.0+/10.0
2. Codeine 138. Bromocodeine**	241/20	161/20	8.04/15.0	8.04/20+	16.0+/10.0

* Slight exaggeration of reflexes but no convulsions; usually very persistent depression.

In the cat convulsions occurred with 20 mg per kg of either chlorocodeine or bromocodeine, but there was no morphine-like excitement. Cats were killed by 20 mg per kg of bromocodeine.

TABLE 22.—*Hydroxyl substitution in the alicyclic portion of the nucleus*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
154. Dihydrocodeinone	86/	47/	4.2/	1.28/	0.86/	2.56+/	0.08/
320. Hydroxycodeinone**	23	23	30+	4.68	[a]	0.85+	[b]
154. Dihydrocodeinone	86/	47/	4.2/	1.28/	0.86/	2.56+/	0.08/
322. Dihydrohydroxycodeinone**	426	426	1.34	1.34	0.89	0.89+	0.10
154. Dihydrocodeinone	86/	47/	4.2/	1.28/	0.86/	2.56+/	0.08/
321. Acetylhydroxycodeinone**	127	91	1.81	2.72	0.90	2.72+	0.27
20. Dihydrocodeine	225/	168/	14.1/	7.20/	6.45/	3.22+/	0.9/
*323. Dihydrohydroxycodeine-A**	950	[c]	100	50+	[d]	[c]	7.71
20. Dihydrocodeine	225/	168/	14.1/	7.20/	6.45/	3.22+/	0.9/
*324. Dihydrohydroxycodeine-B**	650	[f]	13.0	2.50	2.50	20.0	0.37
20. Dihydrocodeine	225/	168/	14.1/	7.20/	6.45/	3.22+/	0.9/
*370. Dihydrohydroxycodeine-C**	575	575	20.0	2.00	2.00	1.00	0.75
51. Dihydroisocodeine	896/	[g]/	29.8/	1.91/	0.98/	0.98+/	0.22/
*323. Dihydrohydroxycodeine-A**	950	[c]	100.0	50+	[d]	[c]	7.71
51. Dihydroisocodeine	896/	[g]/	29.8/	1.91/	0.98/	0.98+/	0.22/
*324. Dihydrohydroxycodeine-B**	650	[f]	13.0	2.50	2.50	20.0	0.37
51. Dihydroisocodeine	896/	[g]/	29.8/	1.91/	0.98/	0.98+/	0.22/
*370. Dihydrohydroxycodeine-C**	575	575	20.0	2.00	2.00	1.00	0.75
367. Acetyldihydrocodeine**	91/	91/	30.0/	4.52/	9.04/	3.63+/	---/---
*391. Diacetyldihydrohydroxycodeine-B**	599	458	14.1	3.52	3.52	2.80+	---/---
367. Acetyldihydrocodeine**	91/	91/	30.0/	4.52/	9.04/	3.63+/	---/---
*392. Diacetyldihydrohydroxycodeine-C**	1000+	560	5.64	1.41	1.41	[h]	---/---
390. Acetyldihydroisocodeine**	114/	67/	6.72/	1.34/	1.00/	2.0+/	---/---
*391. Diacetyldihydrohydroxycodeine-B**	599	458	14.1	3.52	3.52	2.8+	---/---
390. Acetyldihydroisocodeine**	114/	67/	6.72/	1.34/	1.00/	2.0+/	---/---
*392. Diacetyldihydrohydroxycodeine-C**	1000+	560	5.64	1.41	1.41	[h]	---/---
88. Thebaine**	31/	31/	---/---	4.36/	4.36/	0.87+/	---/---
31. Bromocodeinone**	6	3	---	1.00	1.00	[i]	---

[a] No exciting effect with 0.5 to 7.0 mg per kg; convulsions occurred with 5.5, 6.0 and 7.0 mg per kg.
[b] No decrease in respiratory activity with 0.1 to 3.0 mg per kg; reflex activity increased at the higher dose.
[c] Occasionally spasmodic movements with practically no increase in reflexes and no generalized convulsions.
[d] None up to 50.0 mg per kg.
[e] None up to 50.0 mg per kg.
[f] Very slight increase in reflexes but no convulsions.
[g] With fatal doses twitching of muscles, slight increase in reflexes, but no convulsions.
[h] None up to 20.0 mg per kg.
[i] None with 0.5 and 1.0 mg per kg.

TABLE 23.—*Alkyl substitution in the alicyclic portion of the nucleus*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
37. Dihydromorphine	133/491	(a)/(b)	17.7/70.0	0.26/3.56	1.77/8.91	0.17/0.89	0.11/1.7
*399. Methyldihydromorphine**							
20. Dihydrocodeine	225/896	168/(c)	----------	7.20/25.8	6.45/(d)	3.22+/8.96	0.9/(e)
*358. Methyldihydrocodeine**			----------				
123. Dihydromorphinone	84/25	67/25	1.77/3.00	0.17/0.07	0.17/0.10	0.08/0.07	0.011/0.012
*359. Methyldihydromorphinone**							
123. Dihydromorphinone	84/27	67/22	1.77/2.01	0.17/0.17	0.17/0.09	0.08/0.17	0.011/0.021
*413. Ethyldihydromorphinone**							
123. Dihydromorphinone	84/17	67/13	1.77/2.25	0.17/1.33	0.17/0.26	0.08/1.80	0.011/0.10
*419. Isopropyldihydromorphinone**							
123. Dihydromorphinone	84/11	67/5	1.77/0.22	0.17/0.36	0.17/0.04	0.08/0.36	0.011/0.0036
*423. Amyldihydromorphinone**							
154. Dihydrocodeinone	86/55	47/50	3.42/8.00	1.28/1.00	0.86/2.00	2.56+/0.80	0.08/0.3
*357. Methyldihydrocodeinone**							
371. Dihydrocodeinone enol acetate**	81/45	65/45	6.32/15.0	1.35/1.50	0.90/2.00	1.12+/2.00+	0.11/0.073
*400. Methyldihydrocodeinone enol acetate**.							

* Convulsions infrequent with fatal doses.
[b] No apparent convulsant action.
[c] No increase in reflexes or convulsions.
[d] None up to 30.0 mg per kg.
[e] None up to 10.0 mg per kg.

It is convenient to consider together, in spite of chemical dissimilarities, the effects of nuclear substitutions (tables 21, 22, and 23). The decrease in activity with the introduction of a new substituent in the aromatic nucleus was very clear (table 21). The effect of the substitution of an hydroxyl, presumably into position-14 of the molecule, seemed also to be in the direction of decreased activity. In the third series, the nuclear alkylated derivatives, however, the effect may be either a decrease or an increase, a phenomenon for which we have no explanation at present. It can scarcely be due to unexpected structural rearrangements taking place during the interconversions of the members of the series, for these conversions are carried out under extremely gentle conditions. The one exception, the demethylation of methyldihydrocodeinone to methyldihydromorphinone, can be reversed with diazomethane, showing that no structural change has taken place.

Before leaving the question of nuclear substitutions there are three special cases worthy of note. First, the toxicity of bromocodeinone, without great activity in other respects was remarkable. The fatal dose was the same, 6 mg per kg, for mice, rabbits, and cats, and death in each instance occurred very promptly, usually immediately following a tonic convulsion.

Second, the isomeric relationship of the three dihydrohydroxycodeines (Nos. 323, 324, and 370) is not known, but on the basis of the

pharmacological effects it appears that -B and -C are probably the normal products corresponding to the dihydrocodeine-dihydroisocodeine pair and that the -A isomer has resulted from an abnormal reaction, perhaps involving a rearrangement. The difference between the -A and the other two isomers, however, was very much greater than one would expect from such a rearrangement as the shift of an hydroxyl to the 8-carbon (pseudocodeine type).

Of the third and new group of nuclear substitutions, the most active member, methyldihydromorphinone, is being subjected to clinical trial. This substance differed most notably from other morphine derivatives in which analgesia and other activity have been considerably increased, dihydromorphinone and dihydrodesoxymorphine-D for example, in that coincident with greater effectiveness there was not a shortening of the duration of action. The analgesic action of methyldihydromorphinone lasted approximately the same length of time as that of an equally effective dose of morphine itself. In addition, doses up to 7 mg, total subcutaneously in man, have shown no trace of emetic action nor of an effect on respiration. Work with the substance is being continued to establish definitely the minimal effective dosage in man for analgesia and cough relief, and the exact relationship between the duration of analgesic action and of dependence satisfaction.

This group also includes some very striking examples of dissociation of the morphine-like properties. Note, for example, that in amyldihydromorphinone in comparison with dihydromorphinone analgesic effect has been decreased, but depressant, exciting, and respiratory effects have been increased. In the other alkyl derivatives of dihydromorphinone the quantitative changes in these effects are quite different.

6. The Change From Tertiary to Quaternary Nitrogen

Morphine and codeine, and the numerous derivatives of the morphine group, add alkyl halides readily at the tertiary nitrogen atom to form quaternary alkylates. Compounds of this type have occasionally been recommended for medical use, as for example codeine methobromide ("Eucodin"). In the present studies only two such derivatives have been investigated. The pharmacological action of other types of morphine derivatives in which the function of nitrogen has been changed, as the N-oxides, the normorphine and N-alkylnormorphine series, and the morphimethines, will be discussed in a later paper.

TABLE 24.—*Change from tertiary to quaternary nitrogen (63)*

	Toxicity	Convulsant action	General depression	Analgesia	Exciting effect	Emetic action	Respiratory effect
1. Morphine	531/271	531/(a)	6.75/67.7	0.75/67.7	0.57/45.1	0.22/45.1	0.15/(b)
39. Morphine methochloride							
2. Codeine	241/1000	161/1000	36.1/100	8.04/125	8.04/(c)	16.0+/125	1.3/(d)
27. Codeine methochloride							

[a] No apparent increase in reflexes; twitching and spasmodic movements unrelated to stimulation occurred.
[b] Minimal effective dose not determined, but much less effective than morphine as a respiratory depressant.
[c] None up to 150.0 mg per kg.
[d] Minimal effective dose not determined, but much less effective than codeine as a respiratory depressant.

When the change was made from tertiary to quaternary nitrogen in the morphine molecule, in the two instances studied at least, the useful morphine-like effects were very markedly decreased, suggesting the importance of the nitrogen in the reactivity of morphine (or codeine) in the tissues. Like other quaternary bases, morphine methochloride and codeine methochloride exhibited in frogs definite curare-like action (*63*).

Conclusions

1. Muzzling the phenolic hydroxyl of morphine with methyl, ethyl, or benzyl groups sometimes increased toxicity but almost always increased convulsant action and decreased all other morphine-like effects. The result was essentially the same, whatever modifications had been made in other portions of the morphine molecule.

2. Covering the alcoholic hydroxyl of morphine with methyl, ethyl, or acetyl groups or replacing it with ketonic oxygen, hydrogen, or halogen also tended to increase toxicity and convulsant action, and to increase other morphine-like effects as well. The most regular in its effect was hydrogen substitution; the least regular, acetylation and replacement by halogen. The increase in activity was usually accompanied by a decrease in duration of action.

3. Substitution of basic groups for the alcoholic hydroxyl of morphine decreased effectiveness in the resulting compound and in some instances brought about qualitative differences in the pharmacological picture.

4. A spatial shift of the alcoholic hydroxyl group from the morphine (or codeine) to the α-isomorphine (or isocodeine) configuration, or from the β-isomorphine (or allopseudocodeine) to the γ-isomorphine (or pseudocodeine) configuration, generally resulted in an increase in pharmacological action. Functional groups at the 6-position were more effective than the same groups at the 8-position of the nucleus.

5. Opening the ether oxygen bridge of the morphine molecule seemed to decrease its activity, though the effect may have been

complicated by other changes simultaneously produced in the morphine structure.

6. Saturation of the 7, 8- or 6, 7-double bond in morphine and its derivatives resulted in changes in pharmacological action so irregular as to be unpredictable.

7. Substitutions in the aromatic nucleus of the morphine series, as far as studied, seemed to result in decreased pharmacological action.

8. A hydroxyl group at the 14-position (presumably) consistently decreased pharmacological effects. Except for toxicity, the same was true of bromine at this position.

9. Nuclear substitution, alkyl, in the alicyclic ring of morphine increased or decreased effectiveness, depending upon the other structural features present in the molecule. In one such derivative, methyldihydromorphinone, increased activity was not accompanied by a corresponding decrease in duration of action. Some of the members of this group exhibited marked dissociation of the morphine-like properties, different effects being modified quantitatively in some instances in opposite directions.

10. Change from tertiary to quaternary nitrogen in morphine markedly reduced morphine-like effectiveness and increased curare-like action.

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PART II. ATTEMPTS TO SYNTHESIZE SUBSTANCES WITH CENTRAL NARCOTIC AND, IN PARTICULAR, ANALGESIC ACTION

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and

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Introduction

The problem of the relation between chemical structure and physiological action dates back to the beginnings of organic chemistry and has developed since, hand in hand with the growing of this branch of science.

It is obvious and well known that the physical and chemical properties of a compound—melting point, boiling point, solubility in different media, acidity or basicity, and others—are determined by the number of atoms in the molecule, i. e., by molecular weight, and by the arrangement of the atoms within the molecule that we ordinarily represent in a so-called structural formula. These formulas, although an excellent tool in descriptive and experimental organic chemistry, do not give, as a whole, a complete account of the characteristic properties of a given compound. In other words, all predictions as to the physico-chemical properties of a compound based on its formula must involve more or less uncertainty. Nevertheless, it is obvious that these properties of a compound determine the degree of its absorption, its transport and storage in the organism, the place or places of its action, and finally the action itself at or in the cells of a particular organ; in summary, they determine the physiological or biological behavior of a compound in the living organism. Consequently, apart from the complexity of the mechanism of normal vital functions and functions modified by administration of chemicals or drugs, the uncertainty concerning the relation: structural formula-physico-chemical properties, applies also to the relation: structural formula-physiological action. (For very interesting, comprehensive, and enlightening essays on these much-

discussed problems, we wish to refer to two articles by Schulemann (*1*)).

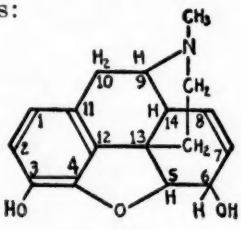
In spite of these uncertainties, the organic chemist has added to the number of drugs obtained by synthetic methods and from natural sources in a merely empirical way, a large number of compounds with great clinical value. The systematic investigation of natural and synthetic products had shown that, within certain relatively limited groups of chemical individuals, a few definite rules as to the relation between formula and action could be found. In many such groups the dependence of a certain pharmacological action upon a certain characteristic feature in the structural formula became obvious and could not be overlooked. As examples among the synthetic products may be mentioned the antipyretics of the phenylpyrazolone group, the vast number of hypnotics of the barbituric acid group, and the local anaesthetics of the alkamine type. For examples among natural products, valuable as chemo- and pharmacotherapeuticals we may point to the group of sex hormones and to the alkaloids of the quinine and morphine groups. Many equally or more valuable substitutes for certain natural products have been obtained by, in principle, minor changes in the molecule, in particular in its functional groups. However, the organic chemist went further and synthesized the torso or characteristic fragments of the natural products, having attached to them the presumably important groups. Thereby the synthetic "substitute" showed sometimes a very close structural resemblance to the original "model;" sometimes such a resemblance could hardly be recognized. The desire for a less toxic local anaesthetic led from cocaine through the eucaines A and B to novocaine and pantocaine; the attempts at finding more effective antimalarials led from quinine through the simple quinoline derivatives, kairin, kairolin, and thallin, to plasmochin and atebrin.

It can be easily seen that the "chemical viewpoint" alone, in spite of the great practical successes, does not bring us nearer to an understanding of the relation between structure and action. On the one hand, chemically very closely related compounds may exhibit enormous differences in effectiveness; for example, trypan blue or germanin in comparison with their respective analogs lacking simply two methyl groups (*2*). On the other hand, compounds with practically no chemical relationship may produce very similar pharmacological effects. We may point out the antipyretic effect of quinine and antipyrine, the analgesic effect of morphine and antipyrine, and finally the central narcosis effected by morphine and the inhalation anaesthetics. The question must remain open, however, whether the final effect, e. g., the analgesic effect of morphine and of antipyrine, is brought about by the same biological process. The necessity of placing the problem—constitution, action—also on a physical basis be-

came obvious and resulted finally in theories that attempt to consider pharmacological effects as the results of physical phenomena (H. H. Meyer, K. H. Meyer, Overton, Traube, Warburg). The experimental work that has been undertaken in this direction is usually arranged for the purpose of establishing correlations between single chemical or physical factors as acidity, distribution effect, surface tension, adsorption, colloidal flocculation, and pharmacological effectiveness within a specific group, *e. g.*, hypnotics (*3*) and local anaesthetics (*4*, *5*). At present, when searching for new compounds of a certain desired action, the chemist must seek, first, for a "model" substance or substances which give him an idea of the direction in which to search. If then, fortuitously, a sufficient number of compounds of practical efficiency have been obtained, a study of the physical properties of these compounds may give a more directed lead to their improvement.

Two principal considerations have instigated the attempts to obtain a morphine substitute by synthetic methods. In the first place, a theoretically definite solution of the drug addiction problem must preassume independence from the manufacture of opium. In the second place, we hope and assume that such synthetic products, which will be probably simpler in their structure than morphine, even if efficient enough, may not bring about addiction or euphoria. This assumption is largely arbitrary, but has a precedent, although not directly comparable, in the synthesis of the simple cocaine substitutes, which do not show the typical intoxication produced by cocaine.

Morphine may be considered as an isoquinoline or a phenanthrene derivative. Adopting for the time being the latter concept, we may analyze the formula picture of morphine as follows: a partially hydrogenated phenanthrene (to be classed as an asymmetric octahydrophenanthrene), carrying besides the phenolic hydroxyl, the alcoholic hydroxyl, and the 4, 5-oxygen bridge, an ethyl-methyl amino chain, $-CH_2-CH_2-N(CH_3)-$, attached in a very unusual way to the positions 13 and 9 of the phenanthrene nucleus.



Morphine.

For this reason it seemed reasonable enough to make first phenanthrene a starting basis and attach to it and its hydrogenated forms successively the functional groups of morphine. Simple phenanthrene derivatives, as hydroxy, amino, and carboxylic acid derivatives and the like were submitted to pharmacological investigation with the hope of a morphine-like action about 30 years ago (Bergell, Pschorr, Schmidt, Vahlen, and others).[1] The results were discouraging and further experimentations in this direction were abandoned.

[1] For a complete bibliography see Fränkel: Arzneimittelsynthese, 6th ed., pp. 412–413.

Although we did not expect to find any useful substances among the simple phenanthrene derivatives (most of the ones mentioned were needed for further synthetic work) we investigated pharmacologically a considerable number of them in order to find out whether or not definite and consistent connections between chemical and pharmacological changes could be observed.

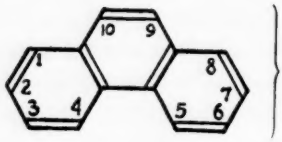
In the first part of this communication, phenanthrene itself, its well-characterized hydro derivatives, and the derivatives carrying the hydroxy, amino, carbonyl, carboxyl group, or a combination of these groups, are discussed. Since the 1- and 4- derivatives of (unhydrogenated) phenanthrene are accessible only with great practical difficulty, this phase of investigation deals chiefly with the phenanthrene derivatives carrying the substituents in position 2, 3, and 9.

The second part comprises a large variety of amino alcohols derived from phenanthrene. This type of compound has been taken up in our program for the reason that morphine may be considered as an amino alcohol containing a tertiary nitrogen and a secondary alcoholic group. Our synthetic amino alcohols may be divided into two groups derived from the fundamentally different types I and II.

Nucleus:

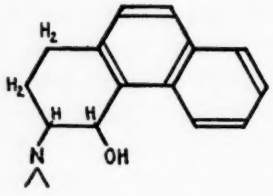
Phenanthrene
9, 10-dihydrophenanthrene
1, 2, 3, 4, 5, 6, 7, 8-octahydrophenanthrene

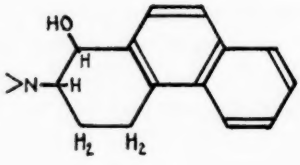
I

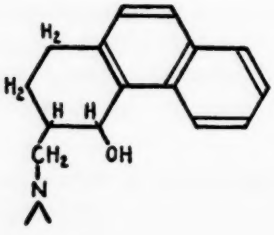


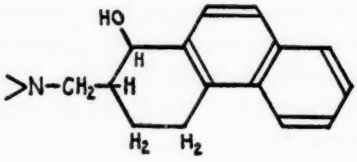
-CHOHCH$_2$N<
-CHOHCH(CH$_3$)N<
-CHOHCH$_2$CH$_2$N<

II



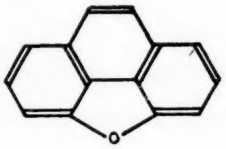






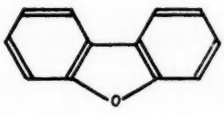
Obviously group II has the greater resemblance to morphine. The most active of our synthetic compounds belong to group II, having an analgesic effectiveness equal to that of some of the morphine derivatives, e. g., pseudocodeine. All of the amino alcohols contain one or two asymmetric carbon atoms. Optical resolutions are planned for some of the members of these groups which show a sufficiently high effectiveness and no undesirable side effects.

The third part of this communication deals with compounds that are derived not from phenanthrene, but from other condensed ring systems. Whether or not the phenanthrene nucleus is essential in bringing about a morphine-like or, in particular, an analgesic action is, at present, an open question. The possibility had to be taken into consideration, that a somewhat similar ring system together with the proper substituents in certain positions may replace the phenanthrene nucleus. Considerations concerning the structure of morphine led to such a system. The ethereal or bridge oxygen in morphine may be as important as the phenolic hydroxyl group. 4, 5-Phenanthrylene oxide (III) itself cannot be synthesized at present. (The 3-hydroxy-4, 5-phenanthrylene oxide can be readily obtained by a degradation process from morphine. See below.) Therefore we chose a structurally similar ring system, namely dibenzofuran (IV) from which we prepared derivatives analogous to those in the phenanthrene series.



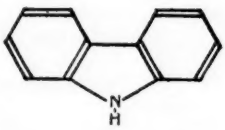
III

4, 5-Phenanthryleneoxide.



IV

Dibenzofuran.



V

Carbazole.

The dibenzofuran derivatives as a whole show slightly higher analgesic activity than the corresponding phenanthrene derivatives, but are, unfortunately, more toxic.

By replacing the oxygen in dibenzofuran by an imino group, we arrive at carbazole (V), which has no relation to phenanthrene or phenanthrylene oxide and is distinctly different from the above discussed ring systems on account of its acid character. Recently some N-acyl derivatives of hexahydrocarbazole and a number of amino

44192°—38——4

alkyl esters of carbazole-N-carboxylic acid have been reported to exhibit hypnotic and local anaesthetic effect respectively (6, 7), whereby in both instances the relatively low toxicity of these compounds became apparent.

So far only a few carbazole compounds carrying amino groups and alkamine side chains have been prepared and tested pharmacologically. Very remarkable with this group of compounds is the relatively low toxicity and the consistent effect of lowering the body temperature together with a relatively high analgesic effect. In this respect there appears to be a superficial resemblance to some members of the phenyl-pyrazolone group.

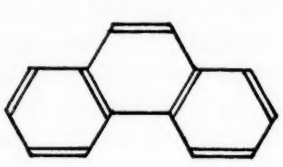
For their pharmacological evaluation, all of the substances have been administered orally to cats, in suspension or dissolved in 2 per cent aqueous acacia solution. Observations have been made for the detection of depressant and analgesic effects, disturbance of coordination, emetic action, and effects on heart and respiratory rates and rectal temperature. For the more soluble and more active substances toxicity and convulsant action in mice have been determined and in a few instances experiments have been carried out on other animals. The general methods and some of the results have been reported previously (Eddy, *8, 9, 10;* Smith, *11;* Eddy, *12, 13, 14, 15*), but the greater part of the data summarized in the tables of this paper is from the protocols of work in progress in the pharmacological laboratory of the University of Michigan.

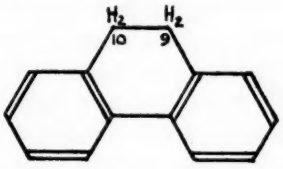
1. Phenanthrene, Hydrogenated Phenanthrenes, and Simple Derivatives

(a) PHENANTHRENE AND ITS HYDRO DERIVATIVES

The experimental material to be described, arranged according to chemical relationships, will be presented in tabular form. In each table is given the substituent or substituents of each compound and the position of attachment to the nucleus, indicated in the table heading. Some of the physical properties of the substances are also given and a summary of the pharmacological results. The following explanation of the data applies throughout: For simplicity of reference, Drug Addiction Laboratory sample numbers are given in the first column. Approximate solubilities have been determined only in the later stages of this work; otherwise the very rough distinction—very soluble (v. s.), soluble (s.), moderately soluble (m. s.), sparingly soluble (s. s.), and insoluble (i.)—has been used. The figures in the columns, analgesia, general depression, incoordination, emesis, and rectal temperature, are mg per kg of the substance as administered, and are in each instance the lowest dose at which the effect indicated was observed. For the first three effects the initials, N., S., M., and Mk. indicate none, slight, moderate, and marked effects at the doses

given. Where N. is used, the dose is the highest administered. Under emesis, if vomiting occurred, the smallest dose with which it was observed is given, also the number of animals of five which vomited (figure in parentheses) and the time in minutes after administration of the drug when vomiting occurred, averaged if more than one animal vomited. Sometimes salivation was the only indication of the emetic effect. This is indicated by the abbreviation, Sal., before the dose with incidence and time given as when vomiting occurred. If vomiting did not occur (N.), the dose is the highest administered. Under rectal temperature the effect is indicated as — (decrease), + (increase), or ± (indecisive). For the first two, the minimal effective dose is given and the maximum deviation from normal, averaged for the group. In the absence of decisive effect, the dose given is the highest administered. Occasionally the ± with a following figure is used when the effect was diphasic.





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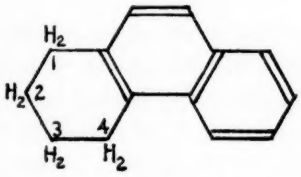

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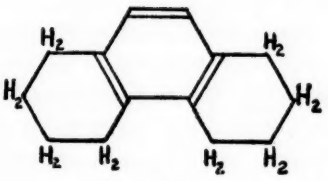


204

TABLE 1*.—*Phenanthrene and its hydro derivatives*

Substance	M. p., °C.	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
6 Phenanthrene	99.5	N 1000	S 300	S 200	200 (1) 68′	[b] 100 (−) 0.5°
355 9, 10-dihydro-	31–32	S 300	S 200	S 300	Sal 300 (1) 60′	200 (−) 0.6°
248 1, 2, 3, 4-tetrahydro-	31–32	[a] Mk 400	S 300	S 300	Sal 400 (2) 90′	400 (−) 1.4°
204 1, 2, 3, 4, 5, 6, 7, 8-octahydro-	Liquid $n_D^{17}=1.5570$	N 1000	S 500	S 500	N 1000	500 (−) 0.7°

*See text for explanation of data.

The solubility of these four compounds is practically the same. They are insoluble in water, soluble in methanol and ethanol, easily soluble in ether, petrol-ether, and olive oil. The tetrahydro- and octahydro-compounds are probably somewhat more easily soluble in olive oil than phenanthrene and its dihydro-derivative.

[a] With 300 mg per kg slight effect in 3 of 5 animals.

[b] Decrease in temperature was only 0.6° with 500 mg per kg.

The level of effectiveness of phenanthrene and its hydro derivatives is low (table 1). In this respect octahydrophenanthrene is most like phenanthrene; tetrahydrophenanthrene is more effective as a depressant and even exhibits some analgesic action; while the dihydrophenanthrene is the most effective of the group. These differences are not paralleled by differences in solubility.

On account of its insolubility, one experiment was run to determine the approximate absorbability of phenanthrene. On March 22, 1933 a medium-sized cat was given, by stomach tube, one gram of phenanthrene, suspended as usual in 2 percent acacia solution. On each of the next 5 days 1½ grams of phenanthrene were given by stomach tube. The latter dose was about 600 mg per kg and the total amount administered was 8.5 grams. The cat showed mild depression after the first 2 days, ate very poorly, and lost weight. The depression continued about 3 days after the last dose of phenanthrene. Then the cat became more lively, its appetite improved, and its appearance rapidly became normal. The feces were collected from the morning of March 22 to the morning of March 31, inclusive, and dried in air.

The feces were of doughy consistency. They were kept in a vacuum desiccator over phosphorus pentoxide for about a week. Then it was possible to pulverize the mass very fine, except for fibers and hairs which were present in quite large quantity.

The entire mass was extracted in a Soxhlet apparatus with petroleum ether (b. p., 25–65°) for 3 days. A yellow-brownish amorphous substance (0.1–0.2 gram) precipitated. This proved to be insoluble in alcohol and acetone.

The greenish colored petroleum ether solution which had still the intense odor of feces was extracted first with dilute (10 percent) hydrochloric acid and then with dilute (5 percent) potassium hydroxide. While no appreciable amount of bases could be found, in the alkaline extraction there precipitated a finely crystalline potassium salt (1.7 grams). The aqueous solution of this salt yielded on acidifying an amorphous oil of intensely rancid odor.

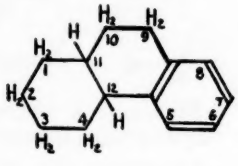
The petroleum ether solution was allowed to stand over charcoal for a day, but neither the odor nor the color could be removed in this way. After evaporating the petroleum ether there was left 6.7 grams of a crystalline substance. Attempts to purify this crude phenanthrene by crystallization failed. By subliming it twice (110–120°) in an oil-pump vacuum, a phenanthrene of m. p. 98–99.5° was obtained. Yield, 5.22 grams (about 2–3 percent may have been lost during the whole procedure). The residue from this sublimation is a heavy brownish oil containing a few crystals, possibly cholesterol-like substances.

The excreta, after extraction with petroleum ether, were extracted for several days with ether. The resulting solution was bright yellow. No bases and no phenanthrene could be detected. The alkaline extraction results in a crystalline bright yellow acidic substance with a distinct rancid smell.

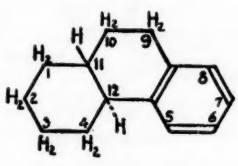
The two acid substances obtained in addition to the phenanthrene were not further investigated.

The 5.22 grams of phenanthrene recovered represented 61.4 percent of the amount administered; or, taking the loss of material during the procedure into account, probably 65 percent escaped absorption. One cannot, of course, exclude the possibility that a part of the recovered phenanthrene had been absorbed and excreted into the intestine but this seems very unlikely. The similarity of physical properties makes it probable that the ratio of absorption would be similar for phenanthrene and its hydro derivatives (table 1).

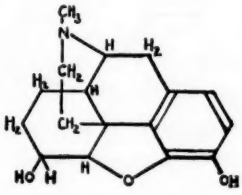
The as.-octahydrophenanthrene, the real skeleton of the morphine alkaloids, has not been included as yet in this investigation, since, owing to technical difficulties, the preparation of a pure (cis or trans) 1, 2, 3, 4, 9, 10, 11, 12-octahydrophenanthrene has not been accomplished (*16*, *17*).



asym. cis Octahydrophenanthrene.



asym. trans Octahydrophenanthrene.



Dihydromorphine.

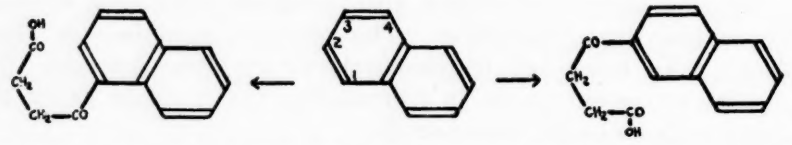
Phenanthrene [2] was purified by the method of Cohen and Cormier (*18*) and subsequent boiling and distillation over sodium. For a

[2] We wish to acknowledge the assistance of the Barrett Co. and the Reilly Tar and Chemical Corporation in providing us with technical phenanthrene.

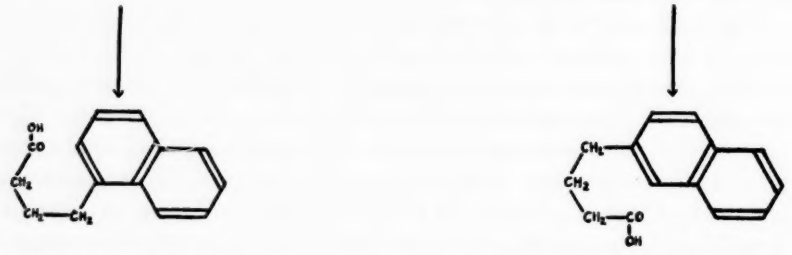
recent very effective purification, see Durland and Adkins (*19*), and compare also Bachmann (*20*).

9, 10-Dihydrophenanthrene was prepared by the method of Burger and Mosettig (*21*) by selective high pressure reduction of phenanthrene with copper-chromium-barium oxide catalyst (*19*).

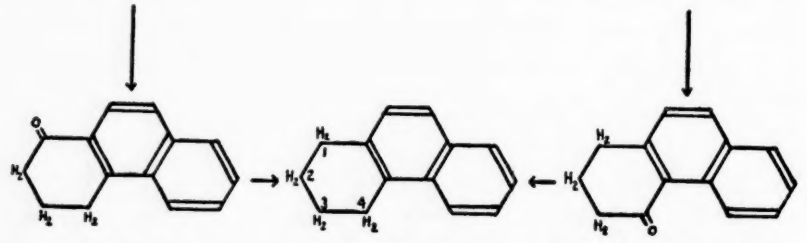
1, 2, 3, 4-Tetrahydrophenanthrene was prepared by high pressure reduction of 4-ketotetrahydrophenanthrene or of a mixture of 1- and 4-ketotetrahydrophenanthrene as obtained by ring closure of a mixture of γ-(1-naphthyl)-n-butyric acid and γ-(2-naphthyl)-n-butyric acid (*22*) according to the method of Haworth (*23, 24*).



β-(1-Naphthoyl)-propionic acid. Naphthalene. β-(2-Naphthoyl)-propionic acid.



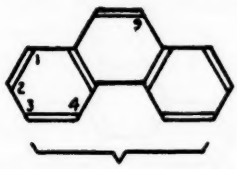
γ-(1-Naphthyl)-n-butyric acid. γ-(2-Naphthyl)-n-butyric acid.



1-Keto-1, 2, 3, 4-tetrahydrophenanthrene. 1, 2, 3, 4-Tetrahydrophenanthrene. 4-Keto-1, 2, 3, 4-tetrahydrophenanthrene.

1, 2, 3, 4, 5, 6, 7, 8-Octahydrophenanthrene was prepared by the method of van de Kamp and Mosettig (*25*) by high pressure reduction of phenanthrene with Raney nickel catalyst (*19*).

(b) MONOHYDROXYPHENANTHRENES



-OH, $-OCH_3$, $-OCH_2CH_3$, $-OCOCH_3$

TABLE 2.—*Monohydroxy phenanthrenes*

Position-substituent	M. p., °C.	Solubility in olive oil*	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
387 1-OH	153–154	s.	N 300	S 100	S 200	N 300	300 (±)
40 2-OH	168–169	s. s.	[a] N 300	S 200	M 300	300 (1) 300′	300 (−) 1.8°
174 2-OCH_3	96	v. s.	N 300	S 200	N 300	Sal 200 (1) 60′	300 (±)
173 2-OC_2H_5	111–112	s.	N 300	S 200	N 300	N 300	300 (−) 0.5°
175 2-$OCOCH_3$	142	v. s.	N 300	S 200	S 300	N 300	300 (±)
41 3-OH	121–123	s.	[b] S 200	S 100	M 300	Sal 300 (3) 120′ [c]	[d] 100 (−) 0.4°
133 3-OCH_3	57–59	s.	N 400	S 300	S 300	N 400	300 (−) 0.7°
176 3-OC_2H_5	45	s.	N 300	S 200	N 300	N 300	300 (±)
72 3-$OCOCH_3$	116	s.	N 300	S 200	S 300	N 300	300 (−) 0.8°
388 4-OH	113–115	s.	[e] N 200	S 100	S 100	100 (1) 108′ [f]	100 (−) 0.7°
105 9-OH	152–153	m. s.	N 300	S 200	S 200	Sal 200 (1) 120′	200 (−) 1.6°

*All of the substances of this table are practically insoluble in water.

[a] Results were suggestive in some animals, but for the group definitely below criterion for minimal effective dose.

[b] Of 10 animals given 300 mg per kg, analgesic effect was marked in 5.

[c] One animal vomited in 5′ with 200 mg per kg, probably the result of local irritation during administration.

[d] The temperature fell 3.0° (average) with 300 mg per kg.

[e] 300 mg per kg given to 2 animals was definitely toxic to one of them.

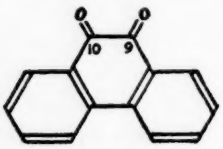
[f] Three animals vomited (average 155′) with 200 mg per kg.

The pharmacological effectiveness of the hydroxyphenanthrenes (table 2) is also low, but the 3-hydroxy derivative stands out clearly as the most active of the group. 4-Hydroxyphenanthrene is second, while the others are so much less effective that the attempt to place them in any order is not only difficult but of little significance. The alkyl ethers and acetyl derivatives are less effective than the free hydroxy compounds. This relationship is like that in the morphine-codeine pair and the pairs of corresponding derivatives in the morphine series (*26*), but the fact that 3-hydroxyphenanthrene among its isomers is the most effective must be regarded as coincidental to the 3-position of the phenolic hydroxyl in morphine.

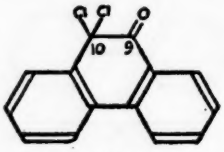
The *2- and 3-hydroxyphenanthrene* were obtained by potassium hydroxide fusion of the barium salts of the corresponding sulfonic acids,[3] according to Fieser, by the modified Werner method (*27*); the

[3] We wish to express our thanks to Merck & Co., Rahway, N. J., for the large-scale preparation of the barium phenanthrene sulfonates used in this research.

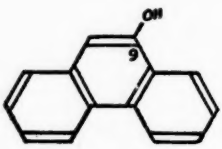
9-hydroxyphenanthrene was prepared from 9, 10-phenanthrenequinone through its dichloro derivative (*28*, *29*, *30*).



9,10-Phenanthrene-quinone.



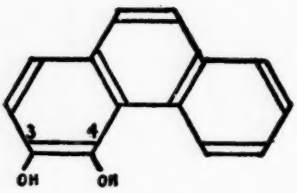
10,10-Dichloro-9-phenanthrone.



9-Hydroxy-phenanthrene.

1- and 4-Hydroxyphenanthrene were prepared by the method of Mosettig and Duvall (*31*) by catalytic dehydrogenation of 1-keto- and 4-keto-tetrahydrophenanthrene, respectively.

(c) POLYHYDROXYPHENANTHRENES AND HYDROXYPHENANTHRYLENE OXIDES



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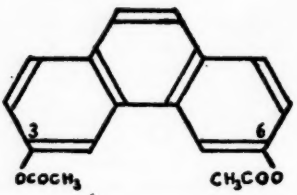

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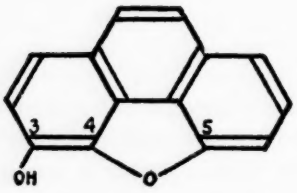

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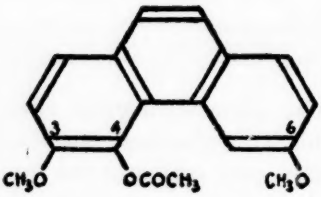


180

TABLE 3

A. POLYHYDROXYPHENANTHRENES

	Position-substituent	M. p., °C.	Solubility in olive oil*	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
177	3-OH, 4-OH	143	s	Mk 150	M 100	M 150	100 (5) 28′	100 (−) 0.9°
178	3-OCOCH$_3$, 4-OCOCH$_3$	156	s	N 300	S 200	N 300	N 300	300 (±)
179	3-OCOCH$_3$, 6-OCOCH$_3$	124	s	S 300	M 200	S 200	Sal 300 (1) 60′	200 (−) 0.9°
180	3 OCH$_3$, 4 OCOCH$_3$, 6-OCH$_3$	118–120	m. s.	N 300	S 200	S 300	200 (1) 46′	200 (−) 0.4°

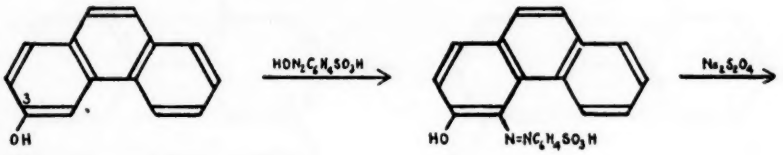
B. HYDROXYPHENANTHRYLENE OXIDES

223	3-OH	144	s	M 300	S 200	S 200	300 (3) 72′	200 (−) 0.8°
200	3-OCH$_3$	65	s	N 400	S 300	N 400	Sal 400 (2) 42′	400 (±)
224	3-OCOCH$_3$	138	s	N 400	S 300	N 400	400 (1) 120′	400 (±)

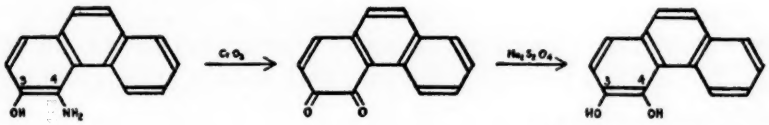
* All of the substances of this table are practically insoluble in water.

The analgesic action of 3-hydroxyphenanthrene is decidedly increased by the introduction of a hydroxyl group into position 4 (table 3–A), but at the same time toxicity and emetic action are also increased. Four cats died with 150 mg per kg of No. 177, two within 5 hours and two within 24 hours. With No. 41 (3-hydroxyphenanthrene), on the other hand, nine animals recovered promptly after 300 mg per kg; a tenth was still markedly depressed at the end of 24 hours and died during the second night.

As with 3-hydroxy- and 2-hydroxy-phenanthrene, acetylation of both hydroxyls of the dihydroxy compound decreased effectiveness decidedly. What difference there is in the action of the two isomeric diacetyl derivatives, No. 178 and No. 179, is slightly in favor of



3-Hydroxyphenanthrene.



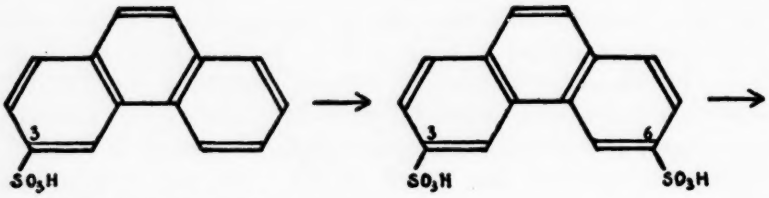
3, 4-Dihydroxyphenanthrene.

No. 179. No. 180, for which no comparison is available, is a rather inactive compound.

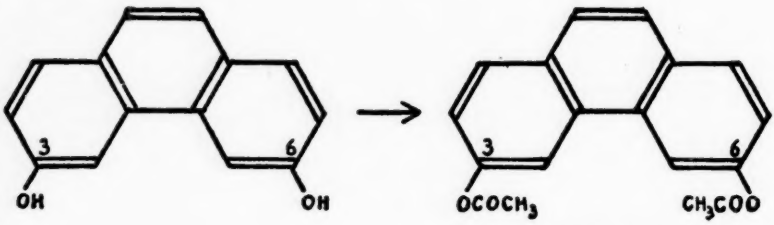
3-Hydroxy-4,5-phenanthrylene oxide exhibited some analgesic action (table 3–B), but less than 3-hydroxyphenanthrene. With the largest dose of No. 223 (300 mg per kg) the pupils were slightly to moderately dilated. Again the effects were decreased by "muzzling" the hydroxyl by either acetylation or methylation. The difference between 3-methoxy- and 3-acetoxy-phenanthrene, on the one hand, and 3-methoxy- and 3-acetoxy-phenanthrylene oxide, on the other hand, is very slight; it is possibly in favor of a greater depressant action in the absence of the oxygen bridge. However, the series of derivatives of phenanthrylene oxide is being continued, these examples being too few to warrant a definite conclusion.

3, 4-Dihydroxyphenanthrene ("morphol") and its diacetyl derivative were prepared by the method of Fieser (*32, 33*) from 3-hydroxyphenanthrene through 4-amino-3-hydroxyphenanthrene and 3, 4-phenanthrenequinone.

3, 6-Diacetoxyphenanthrene was obtained from the corresponding phenanthrene disulfonate (*34*).

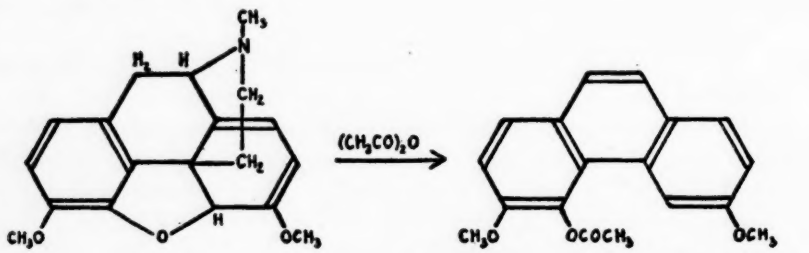


Phenanthrene-3-sulfonic acid.



3, 6-Diacetoxy phenanthrene.

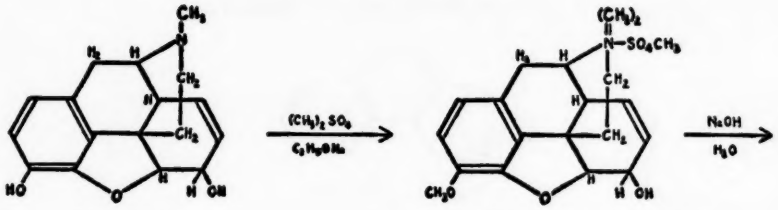
3, 6-Dimethoxy-4-acetoxyphenanthrene ("acetylthebaol") is obtained very conveniently by boiling thebaine with sodium acetate and acetic anhydride (*34*, *36*).



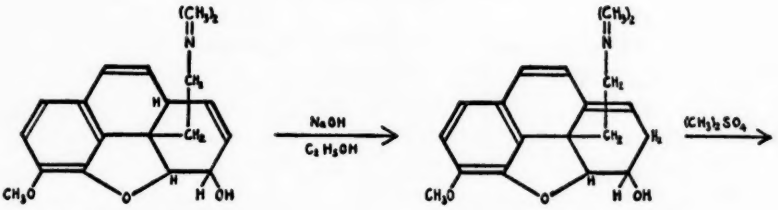
Thebaine.

3,6-Dimethoxy-4-acetoxy-phenanthrene (acetylthebaol).

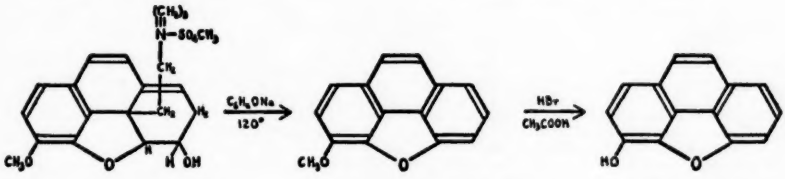
3-Hydroxy-4, 5-phenanthrylene oxide ("morphenol") and its 3-acetoxy- and 3-methoxy derivative ("methylmorphenol") can be prepared conveniently according to Mosettig and Meitzner (*37*) by a modified Vongerichten's degradation process of morphine.



Morphine. Codeine metho-methylsulfate.



α-Methylmorphimethine. β-Methylmorphimethine.



β-Methylmorphimethine methomethylsulfate. Methylmorphenol. Morphenol.

(d) AMINO- AND AMINOMETHYL-PHENANTHRENES

$-NH_2$, $-NHCOCH_3$, $-N(CH_3)_2$, $-CH_2NH_2$

TABLE 4.—*Amino- and aminomethyl-phenanthrenes*

	Position-substituent	M. p., ° C.	Solubility in olive oil	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
114*	2-NH_2	83–84	v. s.	S 100	[a] S 75	M 75	75 (1) 300′ [b]	75 (−) 1.4°
115*	3-NH_2	86	v. s.	S 50	[c] S 50	S 50	50 (1) 317′ [d]	50 (−) 1.0°
116*	3-$NHCOCH_3$	200	s.	N 400	S 200	S 200	N 400	200 (−) 0.5°
356**	3-N $(CH_3)_2$	220–225		N 200	S 100	S 100	100 (2) 90′	200 (−) 0.6°
117*	9-NH_2	135–136	v. s.	N 300	S 100	S 100	100 (1) 330′ [e]	100 (−) 0.8°
122	9-$NHCOCH_3$	207–208	s.	N 300	S 300	S 300	N 300	300 (±)
184***	9-CH_2NH_2	292–294 dec.		S 150	M 100	[f] M 100	100 (3) 28′	200 (−) 1.4°

* Administered as free base. Practically insoluble in water. The hydrochloride is moderately soluble in water but hydrolyzes easily, particularly when heated in solution.
** Administered as hydrochloride. Percent base: 85.8. Immediate hydrolysis in water.
*** Administered as hydrochloride. Percent base: 85.0. Moderately soluble in water.
[a] 3 of 5 animals died within 24 hours with 100 mg per kg.
[b] With 100 mg per kg all 5 cats salivated and 2 vomited, 190′ average.
[c] 2 of 5 animals died within 24 hours with 100 mg per kg.
[d] With 100 mg per kg 3 cats salivated and 1 vomited in 196′.
[e] None of the cats vomited with 200 or 300 mg per kg.
[f] Incoordination of the characteristic delayed relaxation type (*see* 9-carboxylic acid phenanthrenes).

Of the three isomeric aminophenanthrenes (table 4) the 3-amino compound was the most effective in respect to analgesic and depressant effects. It was also quite toxic to the cat. The 2-derivative showed some analgesic effect but was about as toxic and more emetic than its 3-isomer. The 9-derivative, however, had no analgesic action even with much larger doses; up to 300 mg it was not toxic, and its emetic effect was very slight. These aminophenanthrenes increased the respiratory rate moderately in most animals, and again the 3-isomer had the greatest effect. The heart rate was quickened occasionally but never to a marked degree.

Acetylation or methylation of the amino group lowered its effectiveness in all respects including toxicity. The two substances, 3-acetylaminophenanthrene and 3-dimethylaminophenanthrene, were not significantly different. Removal of the amino group from the nucleus, at least in the 9-position (No. 184), increased distinctly the analgesic and emetic effects, probably also the depressant action. This substance was not toxic in the doses administered.

2- and 3-Aminophenanthrene were originally prepared according to Werner's method (*38*) by heating the corresponding hydroxyphenanthrenes with sodium acetate and ammonium chloride in acetic acid.

$$C_{14}H_9OH \xrightarrow[NH_4Cl]{CH_3COONa} C_{14}H_9NHCOCH_3 \rightarrow C_{14}H_9NH_2$$

9-Aminophenanthrene was obtained by Curtius degradation of the 9-carboxylic acid, according to Pschorr and Schröter (*39*).

$$C_{14}H_9COOH \rightarrow C_{14}H_9COOC_2H_5 \rightarrow C_{14}H_9CONHNH_2 \rightarrow C_{14}H_9CON_3 \rightarrow$$

$$C_{14}H_9NHCOOC_2H_5 \rightarrow C_{14}H_9NH_2$$

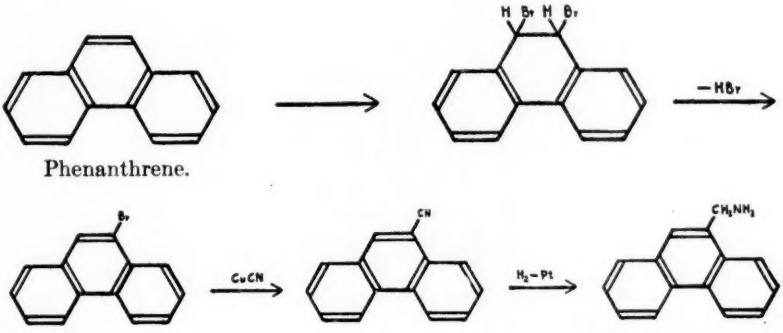
More recently a decidedly more convenient preparative method has been worked out in this laboratory (*40*), by which the three isomeric amines are obtained through the Beckmann rearrangement of the oximes of the corresponding acetylphenanthrenes (*41*).

$$C_{14}H_9COCH_3 \rightarrow C_{14}H_9C{:}(NOH)CH_3 \rightarrow C_{14}H_9NHCOCH_3 \rightarrow C_{14}H_9NH_2$$

3-Dimethylaminophenanthrene may be obtained by methylation of the 3-amino compound with dimethyl sulfate and by thermal decomposition of the quaternary methiodide (*40*).

$$C_{14}H_9NH_2 \rightarrow C_{14}H_9N(CH_3)_3(SO_4CH_3) \rightarrow C_{14}H_9N(CH_3)_3I \rightarrow C_{14}H_9N(CH_3)_2$$

9-Aminomethylphenanthrene was prepared by catalytic hydrogenation (platinum oxide, glacial acetic acid) of 9-cyanophenanthrene (*42*).



Phenanthrene.

9-Aminomethylphenanthrene.

The latter could be conveniently prepared from 9-bromophenanthrene (*43*). Other preparative methods for this amine have been described by Shoppee (*44*) and by von Braun (*45*).

(e) AMINO DERIVATIVES OF DIHYDRO- AND TETRAHYDRO-PHENANTHRENES

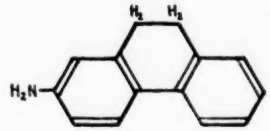


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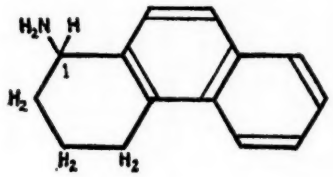
TABLE 5

A. AMINO-DIHYDROPHENANTHRENES

Position-substituent	Percent base	M. p., °C.	Solubility in water	Analgesia	General depression	Convulsions (cat)	Incoordination	Emesis	Rectal temperature	A.F.D.	M.C.D
380 2-NH_2	84.2	323–325 vac. dec.	m. s.[a]	S 100	S 100		[b]S 80	100 (2) 28′	80 (−) 1.2°		
381 2-$N(CH_3)_2$	85.9	186–188	(•)	N 250	S 100		S 100	200 (1) 35′	100 (−) 0.7°		



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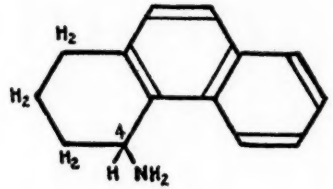


295

B. AMINO-TETRAHYDROPHENANTHRENES

293 1-NH_2	84.4	256 dec	s	M 20	S 25	100 (2) 54′	S 20	20 (2) 53′	15 (+) 0.3° 50 (+) 0.5°	275	225
294 1-$NHCH_3$	85.3	258 dec	s	M 30	S 20	N 50	S 25	25 (1) 39′	20 (+) 0.5°	150	100
326 1-$N(CH_3)_2$	86.1	214–215	20 g in 100 cc	M 25 Inj. S 20	S 25 S 15	50 (2) 62′	S 25 S 15	25 (1) 33′ 15 (1) 20′	25 (−) 0.5°	210	210
295 4-NH_2	84.4	267 dec	s	S 20	S 20	50 (3) 47′	S 20	15 (1) 40′	15 (+) 0.6° 50 (−) 0.8°	200	100
327 4-$N(CH_3)_2$	86.1	202 dec	17 g in 100 cc	M 30 Inj. S 15	S 25 S 15	50 (2) 65′	S 25 S 15	25 (3) 35′ 15 (2) 15′	25 (−) 0.6°	240	170

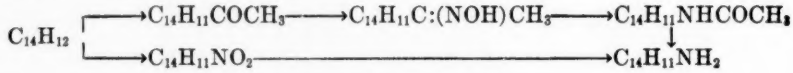
A. F. D. = Average fatal dose. Amount killing more than 50 percent of animals used, administered subcutaneously to mice.
M. C. D. = Minimal convulsant dose. The smallest dose with which convulsions were observed during determination of A. F. D.
vac. = In vacuum. M. p. determined in vacuum.
dec. = Decomposition. Substance decomposed on heating or melted with decomposition.
inj. = Intramuscular injection. Where this abbreviation precedes the analgesic dose, all the data in the same horizontal line refer to the effects of this mode of administration.
Under the heading, "convulsions (cat)" the figures are derived as for the "emesis" column: The first figure is the minimal dose at which convulsions occurred; in parenthesis is the number of animals of five that had convulsions; and the last figure is the time in minutes after administration of the drug when convulsions appeared, averaged if convulsions occurred in more than one animal.
All of the data of this table refer to the hydrochlorides in which form the substances were administered.
[a] Hydrolyzes on heating.
[b] Weakness in hind quarters and staggering unusually pronounced in relation to other effects.
[c] Hydrolyzes strongly.

The dihydro derivatives.—The primary amino compound (380) was more effective than its tertiary dimethyl derivative (381) (table 5A). The former was very similar to 2-aminophenanthrene (114, table 4), except that it seemed to be less toxic. Number 380 was less active than 1- or 4-amino 1, 2, 3, 4-tetrahydrophenanthrene, or 3-aminophenanthrene. The 2-dimethylamino-9,10-dihydrophenanthrene did not reach by far the effectiveness of 1-dimethylamino- or 4-dimethylamino-tetrahydrophenanthrene, but a conclusion relative to the effect of the degree of hydrogenation (dihydro and tetrahydro) is not permissible since the substituents are in different nuclear positions.

The tetrahydro derivatives.—The amines of this group had a rather high analgesic action, but the minimal analgesic and the minimal convulsant dose were in three cases (Nos. 326, 295, and 327) close together, while the minimal emetic doses for the group coincided with, or were even lower than, the minimal analgesic doses. The primary amines appeared to be slightly more analgesic than the corresponding secondary and tertiary. There seemed to be a species difference in respect to convulsant action. In cats this was as great or greater with the tertiary than with the primary amine; in mice, on the other hand, convulsant action was less with the tertiary than with the primary amine. In the main there seemed to be no noteworthy distinction between the 1-series and the 4-series, except for a possible difference in rates of absorption. Orally, the 1-dimethylamino derivative was more analgesic than the 4-dimethylamino; intramuscularly, the 4-dimethylamino compound was the more effective. The latter was probably more emetic both orally and intramuscularly.

Again in this series of amino derivatives there was considerable increase in the respiratory rate with little or no change in heart rate. General depression in the sense of motor quiet was not marked and often there was an initial rise in rectal temperature, usually of brief duration. Generally, as the dose increased, the initial rise in temperature was less apparent and might be succeeded or replaced by a slight fall.

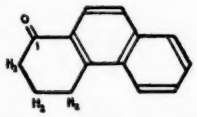
2-Amino-9,10-dihydrophenanthrene can be readily prepared by the Beckmann rearrangement of the oxime of 2-acetyl-9,10-dihydrophenanthrene (*46*). It has been prepared recently in crystalline form, m. p. 53–54°, by reduction of the corresponding nitro compound (m. p. 81–82°) which could be obtained in satisfactory yields by nitration of 9,10-dihydrophenanthrene (*47*).



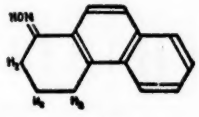
2-Dimethylamino-9,10-dihydrophenanthrene can be conveniently prepared by exhaustive methylation of the amino compound and subsequent thermal decomposition of the methiodide (*46*).

$$C_{14}H_{11}NH_2 \longrightarrow C_{14}H_{11}N(CH_3)_3(SO_4CH_3) \longrightarrow C_{14}H_{11}N(CH_3)_2I \longrightarrow C_{14}H_{11}N(CH_3)_2$$

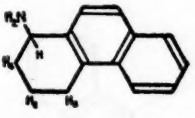
1- and 4-Amino- 1, 2, 3, 4-tetrahydrophenanthrene were prepared by sodium or aluminum amalgam reduction of the oximes of 1- and 4-oxo-1, 2, 3, 4-tetrahydrophenanthrene. The methyl- and dimethylamino compounds were prepared in the customary way (*48*).



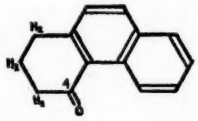
1-Keto-1, 2, 3, 4-tetrahydrophenanthrene.



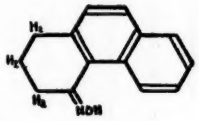
Oxime.



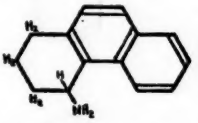
1-Amino-1,2,3,4-tetrahydrophenanthrene.



4-Keto-1, 2, 3, 4-tetrahydrophenanthrene.



Oxime.



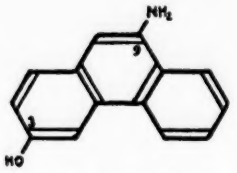
4-Amino-1,2,3,4-tetrahydrophenanthrene.

$$C_{14}H_{13}NH_2 \xrightarrow[CH_3COONa]{CH_3I} C_{14}H_{13}N(CH_3)_2$$

$$C_{14}H_{13}NH_2 \longrightarrow C_{14}H_{13}N{=}CHC_6H_5 \longrightarrow$$

$$C_{14}H_{13}N(CH_3I){=}CHC_6H_5 \xrightarrow{H_2O} C_{14}H_{13}NHCH_3 \text{ (Method of Decker)}$$

(f) HYDROXYAMINOPHENANTHRENES



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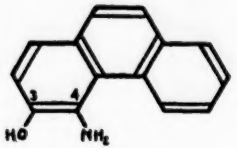

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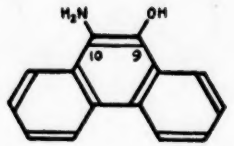


203

TABLE 6.—*Hydroxyaminophenanthrenes*

Position-substituent	Percent base	M. p., ° C.	Solubility	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
145* 3-OH, 9-NH_2	85.2	dec.	s. s. (water)*	N 400	S 200	S 200	N 400	200 (−) 0.5°
42* 3-OCH_3, 9-NH_2	85.9	dec.	s. s. (water)*	[b] N 300	S 300	S 300	[a] 200 (3) 40′	300 (−) 0.7°
94** 3-OCH_3, 9-$N(COCH_3)_2$	100	149–150	s. s. (olive oil)	N 500	S 300	S 500	500 (1) 300′	300 (−) 0.5°
183* 3-OH, 4-NH_2	85.2	dec.	s. s. (water)*	S 150	[d] S 100	S 100	[a] 100 (3) 28′	100 (−) 0.6°
203* 9-OH, 10-NH_2	85.2	dec.	(f)	N 300	S 200	S 300	[a] 200 (4) 16′	[h] 200 (+) 0.9°
75* 9-OCH_3, 10-NH_2	85.9	220–228 dec.	s. s. (water)*	[c] N 300	S 100	S 100	N 300	100 (−) 1.1°
73** 9-OH, 10-$NHCOCH_3$	100	217–218	s. s. (olive oil)	N 500	S 300	S 300	N 500	300 (−) 0.5°
74** 9-OCH_3, 10-$NHCOCH_3$	100	249–250	s. s. (olive oil)	N 500	[e] S 200	S 200	N 500	300 (−) 0.5°
95** 9-OC_2H_5, 10-$NHCOCH_3$	100	247	s. s. (olive oil)	N 400	S 300	S 300	N 400	400 (−) 0.5°

[a] All data refer to the hydrochloride in which form the substance was administered.
[aa] Administered as free base. Practically insoluble in water.
[c] Hydrolyzes.
[b] Results with 300 mg per kg suggestive but below criterion for minimal effective analgesic dose.
[e] None of 10 animals receiving 300 mg per kg vomited.
[d] Two of five cats died during night, after 200 mg per kg.
[e] Five cats vomited in 28′, average, with 150 mg per kg, and 3 vomited in 17′, average, with 200 mg per kg. All animals receiving this substance salivated profusely. The early vomiting probably interfered with complete absorption.
[f] Hydrolyzes in cold and warm water.
[g] With 300 mg per kg 4 cats vomited in 7½′, average.
[h] Increase in temperature was of brief duration. Temperature was usually normal again at 5 hours, rarely below normal at that time. The rise was less and the secondary decrease more in evidence with 300 mg per kg.
[i] With largest dose, 500 mg per kg, cats resented handling but were quiet in cage; the temperature fell in each of the five, 0.6° average.

Of the three isomeric hydroxyaminophenanthrenes (Nos. 183, 145, and 203, table 6), effectiveness stands in the order named. 3-Hydroxy-4-aminophenanthrene was also the most toxic and quite emetic. The 9-hydroxy-10-aminophenanthrene, which as Vahlen's "morphigenine" has some historical interest (*52*, *53*), seemed to be the least effective, but in this case, as perhaps also with No. 183, early vomiting probably interfered with full development of action.

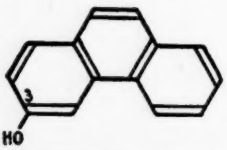
Methylation of the hydroxyl, with another substituent present (145→42; 203→75; 73→74), seemed not to decrease effect; indeed there was some indication that analgesic action might be increased slightly by the change. On the other hand, acetylation of the amino group, with another substituent present (42→94; 203→73; 75→74), did decrease effect. The replacement of a methoxyl by an ethoxyl group (74→95) made no significant difference.

The slight differences between the 3, 9-series and the 9, 10-series are probably not significant. No. 75 had slightly more depressant effect than No. 42; No. 74 slightly more than No. 94. No. 203 was more emetic than 145, but 42 and 94 were more emetic than 75 and 74, respectively.

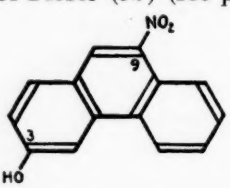
The influence of single substituents on each other, as reflected in changed pharmacological action, was studied in a series of related phenanthrene derivatives with the following results: 3-Hydroxy-9-aminophenanthrene was less active in all respects than the 3-hydroxy compound, and less depressant than the 9-amino; 3-methoxy-9-aminophenanthrene was less depressant than either the 9-hydroxy or 9-amino compounds, but more emetic, which perhaps makes the comparison invalid; 3-hydroxy-4-aminophenanthrene, however, was more analgesic, toxic, and emetic than the 3-hydroxy derivative. A comparison with 4-aminophenanthrene is not available, but 3-hydroxy-4-amino- was less effective than 3-aminophenanthrene. In at least three cases out of four, then, the entrance of the second substituent has rendered the compound less effective than those carrying either substituent alone.

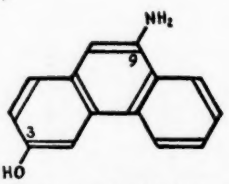
The 3-hydroxy-9-aminophenanthrene was prepared from 3-phenanthrol and elucidated in its structure by Burger and Mosettig (*49*). See also Werner (*50*).

The 3-hydroxy-4-aminophenanthrene may be very conveniently prepared by the method of Fieser (*32*) (see p. 49).



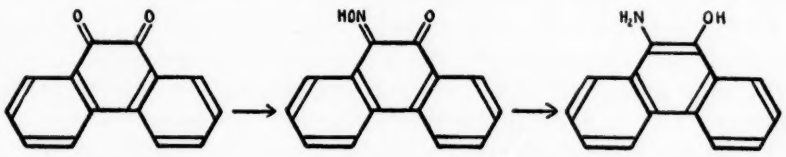
3-Hydroxyphenanthrene.





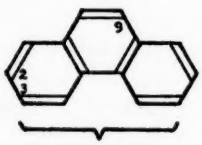
3-Hydroxy-9-aminophenanthrene.

The 9-hydroxy-10-aminophenanthrene was obtained from 9, 10-phenanthrenequinone monoxime according to Schmidt (*51*). Compare also Pschorr (*52*), and Vahlen (*53*).

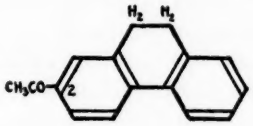


9, 10-Phenanthrenequinone. Monoxime. 9-Hydroxy-10-aminophenanthrene.

(g) ALDEHYDES, KETONES, AND CARBINOLS OF PHENANTHRENE AND HYDROPHENANTHRENES



-CHO, -$COCH_3$, -$COCH_2CH_3$
-CH_2OH, -$CHOHCH_3$



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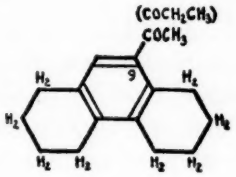


253 (254)

TABLE 7.—*Aldehydes, ketones, and carbinols of phenanthrene and hydrophenanthrene*

Position-substituent	M. p., °C.	Solubility in olive oil*	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
185 3-CHO	79–80	s.	N 300	S 200	S 300	N 300	200 (−) 0.4°
186 9-CHO	100–101	s.	N 300	S 200	[a] S 200	N 300	[b] 200 (+) 0.5°
7 2-$COCH_3$	143	s. s.	[c] N 300	S 200	N 300	N 300	
8 3-$COCH_3$	72	v. s.	S 400	S 100	S 100	400 (3) 300′	400 (±)
101 9-$COCH_3$	74. 5	s.	N 300	S 200	[d] M 300	300 (1) 143′	200 (−) 0.8°
181 3-$COCH_2CH_3$	53–54	v. s.	S 400	S 200	S 200	N 400	200 (−) 0.4°
330 2-$COCH_3$, 9, 10-dihydro-	51–52	s.	[e] N 300	S 200	S 300	300 (2) 14′	300 (−) 1.0°
253 9-$COCH_3$, 1, 2, 3, 4, 5, 6, 7, 8-octahydro-	58–59	s.	[f] N 300	S 200	S 400	N 400	200 (−) 0.5°
254 9-$COCH_2CH_3$, 1, 2, 3, 4, 5, 6, 7, 8-octahydro-	52. 5–53	s.	N 400	S 300	N 400	300 (2) 77′	300 (−) 0.9°
187 3-CH_2OH	103–103. 5	s.	[g] N 300	[h] M 200	[h] M 200	300 (1) 80′	200 (−) 0.5°
188 9-CH_2OH	149–149. 5	s.	N 300	S 200	[i] Mk 200	300 (1) 55′	300 (−) 0.6°
119 2-$CHOHCH_3$	134. 5–135. 5	v. s.	N 300	S 200	S 300	N 300	300 (−) 0.6°
120 3-$CHOHCH_3$	83–83. 5	v. s.	S 200	M 200	M 200	300 (3) 200′	200 (−) 0.6°
118 9-$CHOHCH_3$	135. 5–136	v. s.	N 300	S 300	[j] S 300	N 300	300 (−) 0.5°

*All of the substances of this table are practically insoluble in water.

[a] With 500 mg per kg (1 animal), typical delayed relaxation developed in 2 hours (see carboxylic acid derivatives for description). With smaller doses only slight muscular weakness was seen.

[b] Of the 10 animals used (200 and 300 mg per kg), 6 showed a slight rise, 1 a slight fall, and 3 no change in rectal temperature.

[c] Frequently animals seemed more sensitive to pain after administration.

[d] With 500 mg per kg, each of 3 animals showed typical delayed relaxation. This had disappeared in 24 hours but the 3 cats died during the third 12 hours. With 300 mg per kg, typical delayed relaxation could not be recognized.

[e] Result suggestive in 3 animals, but for the group below criterion for minimal analgesic dose.

[f] Result suggestive in 2 animals with 400 mg per kg.

[g] Result suggestive in 3 animals at this dose, but below criterion for minimal analgesic dose.

[h] Depressant effect and disturbance of coordination developed slowly being most marked 5 hours after administration.

[i] Typical delayed relaxation.

[j] Typical delayed relaxation in 1 animal with 500 mg per kg, but its appearance was delayed until about 12 hours after administration.

The two aldehydes (Nos. 185 and 186, table 7) were alike in their depressant effect and their lack of analgesic action; they differed in that No. 186 caused a peculiar disturbance of coordination, and did not have a lowering effect on rectal temperature.

Of the isomeric acetylphenanthrenes, the one with the substituent in the 3-position was again the most effective, and again delayed relaxation appeared when the substituent was in the 9-position. 3-Acetyl- and 3-propionyl-phenanthrene were practically identical in their effects, except for the late appearance of vomiting with the former. They were probably slightly more effective than phenanthrene-3-aldehyde. The introduction of the acetyl or propionyl group into a hydrophenanthrene did not produce compounds significantly different from those in which the nucleus was not hydrogenated. Throughout the group of ketones, depressant effect and disturbance of coordination were more prominent than analgesic action.

Except phenanthryl-3-methyl carbinol (No. 120), the carbinols and methyl carbinols are not materially different from the corresponding aldehyde and acetyl compounds. No. 120 has the greatest analgesic action, especially in relation to its other effects, of this whole group.

Phenanthrene-2- and -3-aldehydes were obtained by Rosenmund's catalytic reduction of the corresponding acid chlorides (*54*).

$$C_{14}H_9COOH \xrightarrow{SOCl_2} C_{14}H_9COCl \xrightarrow[Pd]{H_2} C_{14}H_9CHO$$

The acetyl[4] *and propionyl compounds* were prepared by the Friedel-Crafts reaction on the respective hydrocarbons. In phenanthrene itself the acetyl and propionyl group enters chiefly position 3 and to a minor extent position 2 (*55*, *56*).

9-Acetylphenanthrene is not formed in the Friedel-Crafts reaction and had to be synthesized by the Claisen condensation of the 9-carbomethoxy derivative with ethyl acetate, followed by hydrolysis of the keto ester (*57*). It can be obtained in a somewhat simpler way by the reaction of 9-cyanophenanthrene with methylmagnesium halide (*41*).

$$C_{14}H_9COOCH_3 \xrightarrow[Na]{CH_3COOC_2H_5} C_{14}H_9COCH_2COOC_2H_5 \xrightarrow{\text{dil. } H_2SO_4} C_{14}H_9COCH_3$$

$$C_{14}H_9CN \xrightarrow[CH_3MgI]{} C_{14}H_9COCH_3$$

In 9, 10-dihydrophenanthrene the *acetyl* and *propionyl* group enters exclusively position 2 (*25*).

The phenanthryl methyl alcohols may be readily obtained by catalytic reduction of the corresponding aldehydes using a platinum oxide catalyst (*54*).

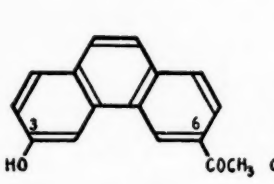
[4] We wish to express our thanks to Merck & Co., Rahway, N. J., for the large-scale preparation of 2- and 3-acetylphenanthrene.

The phenanthryl methyl carbinols are obtained by catalytic reduction of the corresponding acetylphenanthrenes by using either a platinum oxide catalyst under ordinary conditions or a chromite catalyst in Adkins' apparatus at elevated temperatures (*57*).

$$\left.\begin{matrix}\text{-CHO}\\ \text{phenanthrene-COCH}_3\\ \text{-COCH}_2\text{CH}_3\end{matrix}\right\} \xrightarrow{H_2} \begin{matrix}\text{-CH}_2\text{OH}\\ \text{phenanthrene-CHOHCH}_3\\ \text{-CHOHCH}_2\text{CH}_3\end{matrix}$$

(h) HYDROXYACETYLPHENANTHRENES AND CYCLIC KETONES OF TETRAHYDRO- AND OCTAHYDRO-PHENANTHRENES

TABLE 8



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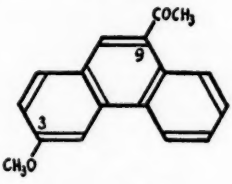

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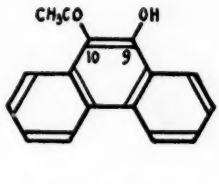
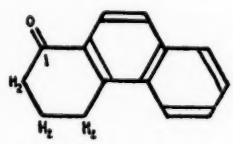


144

A. HYDROXYACETYLPHENANTHRENES

Position-substituent	M. p., °C.	Solubility in olive oil*	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
201 {3-OH, 6-$COCH_3$}	180–181	m. s.	N 300	S 300	N 300	N 300	300 (±)
249 {3-OCH_3, 6-$COCH_3$}	107–108	s.	N 400	S 300	S 400	N 400	300 (−) 0.5°
182 {3-OCH_3, 9-$COCH_3$}	98–99	s.	N 300	S 200	S 200	N 300	300 (±)
144 {9-OH, 10-$COCH_3$}	101.5–102	v. s.	N 400	S 200	N 400	N 400	400 (−) 0.7°



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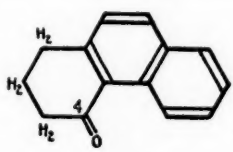

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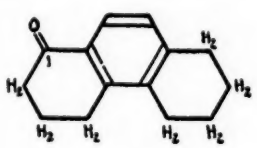


227

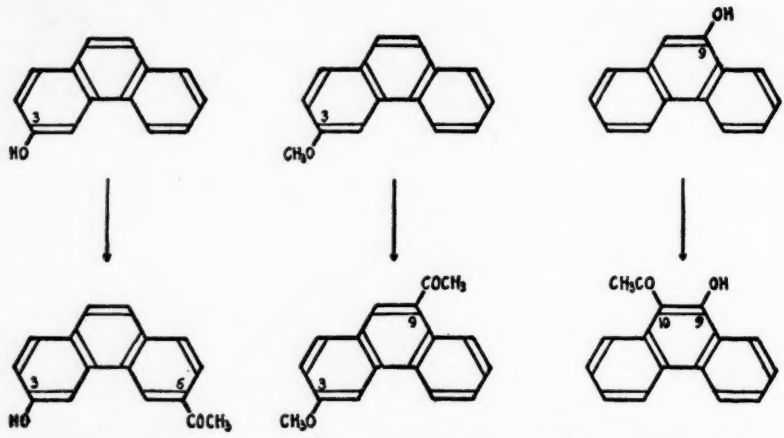
B. CYCLIC KETONES OF TETRAHYDRO- AND OCTAHYDRO-PHENANTHRENE

Position-substituent	M. p., °C.	Solubility in olive oil*	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
225 1-oxo-1, 2, 3, 4-tetrahydro-	95–96	s.	M 400•	S 200	S 400	400 (2) 43′	400 (−) 0.8°
226 4-oxo-1, 2, 3, 4-tetrahydro-	67	s.	N 400	S 200	S 400	400 (1) 33′	200 (−) 0.7°
227 1-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydro-	81–82	s.	N 400	S 200	N 400	400 (2) 3′	200 (+) 0.3°

*All of the substances of this table are practically insoluble in water.
• The effect was greatest 5 hours after administration.

In the series of the hydroxyacetyl compounds there seemed to be but little difference in the effectiveness of the single members. None of the four could be regarded as definitely analgesic. All of them were slightly depressant. Uniformly, all four compounds were slightly less effective in analgesia, general depression, and incoordination than the corresponding compounds carrying only one of the two substituents.

3-Hydroxyphenanthrene was more analgesic and depressant, 3-acetylphenanthrene more depressant than 3-hydroxy-6-acetylphenanthrene. The difference between the 3-methoxy- and the 9-acetylphenanthrenes on the one hand, and the 3-methoxy-9-acetyl compound on the other, was not so marked, the disubstituted phenanthrene being only slightly less active in incoordination and decrease



3-Hydroxy-6-acetyl-phenanthrene. 3-Methoxy-9-acetyl-phenanthrene. 9-Hydroxy-10-acetyl-phenanthrene.

of temperature effects than either of the monosubstituted products. Similarly, hardly any difference could be noticed between the 9-hydroxy- and the 9-acetyl- compounds on the one hand, and the 9-hydroxy-10-acetylphenanthrene on the other.

An explanation for the decrease in effectiveness of the disubstituted products cannot be offered. Undoubtedly the entrance of a phenolic hydroxyl into an acetyl compound, or an acetyl into a phenol, results in a compound more acidic in nature.

The "ring ketones," carrying the carbonyl group within the ring, cannot be structurally compared with the acylphenanthrenes carrying the -CO in the side chain. They can be, to some extent, regarded as acylnaphthalenes. The three members of this group showed only slight activity. Relatively most active was No. 225. It was particularly interesting on account of its mounting analgesic effect.

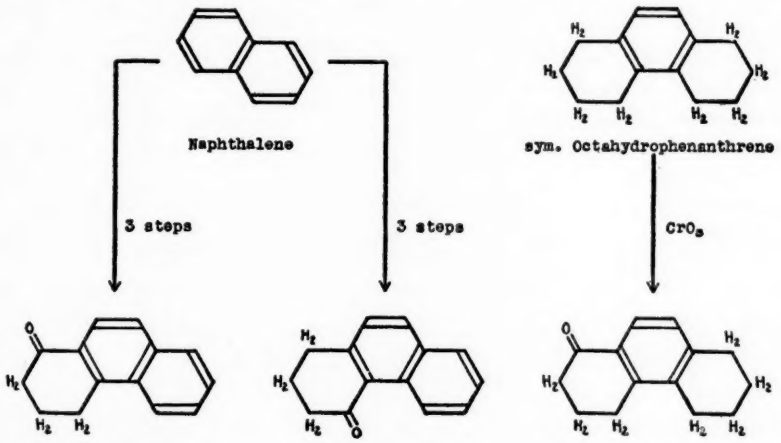
The 4-isomer was not analgesic but was at least as depressant as the 1-isomer.

A similar relationship held between the compounds No. 225 and 227.

It may be pointed out, although no correlation shall be indicated, that of the three cyclic ketones only the 1-ketotetrahydrophenanthrene exerts a slight oestrogenic activity (*58*, *59*).

The hydroxyacetylphenanthrenes listed in table 8A have been synthesized and structurally elucidated in this laboratory. The 3-hydroxy group directs, in the Friedel-Crafts reaction, the acetyl group into position 6, the 3-methoxy group into position 9, and the 9-hydroxy group into position 10 (*60*, *49*).

1- and 4-Keto-1, 2, 3, 4-tetrahydrophenanthrene were prepared according to the method of Haworth (*23*), and 1-keto-1, 2, 3, 4, 5, 6, 7, 8-octahydrophenanthrene according to the directions of Schroeter (*61*) by chromic acid oxidation of octahydrophenanthrene.

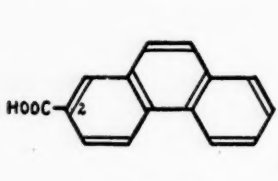


1-Keto-1, 2, 3, 4-tetrahydrophenanthrene.

4-Keto-1, 2, 3, 4-tetrahydrophenanthrene.

1-Keto-1, 2, 3, 4, 5, 6, 7, 8-octahydrophenanthrene.

(i) PHENANTHROIC ACIDS, PHENANTHRYL PROPIONIC ACID, AND DERIVATIVES



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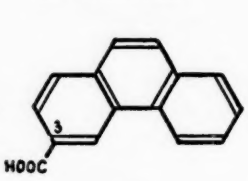

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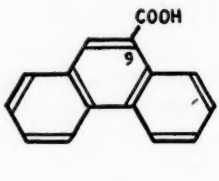

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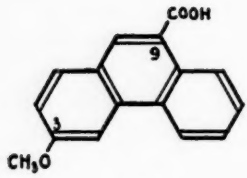

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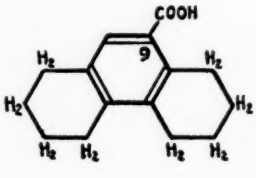

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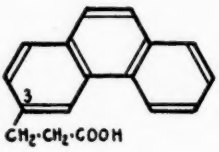

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TABLE 9.—*Phenanthroic acids, phenanthryl propionic acid and derivatives*

	Position-substituent	M. p., ° C.	Solubility in olive oil	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
103	2-COOH[a]	258. 5–260	s. s.	N 300	S 200	S 300	N 500	300 (−) 0. 5°
71	2-COOCH$_3$	96	s.	N 400	S 300	N 400	Sal 300 (1) 300′	300 (−) 0. 5°
9	2-CONH$_2$	242–243	s. s.	N 300	S 100	N 300	N 300	
102	3-COOH[a]	269–270	s. s.	S 100	S 100	S 100	Sal 100 (2) 90′	100 (−) 0. 7° 200 (−) 1. 3°
70	3-COOCH$_3$	95	s.	N 300	S 200	N 300	N 300	200 (−) 0. 5°
10	3-CONH$_2$	233–234	s. s.	N 300	S 200	N 300	N 300	
121	3-CON(CH$_3$)$_2$	120. 5–121	s.	S 100	S 100	M 100	Sal 100 (2) 60′	100 (−) 0. 8°
104	9-COOH[a]	252–254	s. s.	N 300	M 200	[b] S 100	N 300	200 (−) 0. 7°
13	9-COOCH$_3$	116	s.	N 300	M 200	S 200	N 300	
11	9-CONH$_2$	232–233	s. s.	N 300	S 200	[c] S 300	N 300	
328	3-COOCH$_2$CH$_2$N(C$_2$H$_5$)$_2$[d]	202–202. 5	[e]	M 300	[f] S 100	S 150	100 (1) 2′ 200 (1) 13′ 300 (2) 36′	200 (−) 0. 5° 300 (−) 1. 4°
329	9-COOCH$_2$CH$_2$N(C$_2$H$_5$)$_2$[d]	171-171.5	[e]	S 100	S 100	[g] S 25	100 (1) 15′	200 (±)
222	3-OCH$_3$ 9-COOH	200	s. s.	N 200	S 100	[g] S 250	Sal 200 (2) 300′	100 (−) 0. 5°
202	9-COOH 1, 2, 3, 4, 5, 6, 7, 8-octahydro-[i]		[e]	M 150	[h] S 50	[g] M 50	200 (1) 35′	200 (−) 0. 9°
250	3-CH$_2$CH$_2$COOH	154–155	s.	S 300	[j] M 200	M 200	200 (4) 33′	200 (−) 0. 5°
251	3-CH$_2$CH$_2$COOCH$_3$	61–62	v. s.	N 400	S 300	S 300	400 (1) 112′	200 (+) 0. 8°
252	3-CH$_2$CH$_2$CONH$_2$	161–162	m. s.	[k] N 300	S 200	S 300	N 300	300 (−) 0. 3°

[a] The sodium salts (3- and 9- are readily, 2- moderately soluble in water) did not differ in their effects from the free acid.
[b] See text for description of incoordination, typical of this and other 9- derivatives.
[c] With 400 mg per kg there is but a trace of the veratrine-like delayed relaxation.
[d] The data refer to the hydrochloride in which form the substance was administered.
[e] Soluble in water.
[f] With 300 mg per kg 2 of 5 animals died within 12 hours.
[g] Typical veratrine-like delayed relaxation.
[h] The data refer to the sodium salt in which form the substance was administered.
[i] With 200 mg per kg 4 of 5 animals died, 1 within 5 hours, the others 12 to 24 hours after administration.
[j] With 300 mg per kg 1 of 5 animals died within 5 hours.
[k] Results suggestive in 3 animals, but for the group less than criterion for minimal analgesic dose.

Of the three isomeric phenanthroic acids, the 3-acid was the most active, especially in analgesic effect. The order of decreasing effectiveness, 3-, 9-, 2-position, holds for all effects except incoordination. Activity was decreased, in the 3-isomer particularly, but generally also in the other two, by ester formation and by the formation of the primary amide. By converting the primary into the tertiary acid amide, the original effectiveness in all respects was restored (verified for the 3-isomer only).

One would assume that the lipoid solubility (in the case of the 3-isomer) would increase from acid to ester, and from primary to tertiary acid amide; but the effect observed is an opposite one, a decrease in activity in the first, an increase in activity in the second case.

The most characteristic phenomenon observed in connection with the carboxylic acid derivatives was the peculiar disturbance of coordination, which has been described (*8*) as a veratrine-like effect. An hour or more after administration, if an animal was made to jump from a table, it landed with the front paws still drawn up and the hind legs extended as at the beginning of the leap. Its normal position was regained slowly. If the animal was dropped onto the floor, as soon as its toes touched, the hind legs extended and the animal fell on its side with its body in the "leaping" position. Definite evidence of increased reflexes, other than this prompt extension of the hind legs when pressure was put on the toes, could not be elicited. The same phenomenon could be observed in rabbits after administration of phenanthrene-9-carboxylic acid. In cats, it has been seen after many other 9-position phenanthrene derivatives, but never with the 2- or 3-acid, nor with any phenanthrene compound in which the substituent was other than in the 9-position. With doses of 200 and 300 mg per kg of the 9-acid, the effect persisted for 24 to 72 hours, the animal eventually recovering. It was exhibited in much less degree with the methyl ester and only slightly with the acid amide. The site of this peculiar delayed relaxation was investigated by Smith (*11*), who concluded that it was peripheral and on the muscle itself, since it could be elicited on direct and indirect stimulation with the sciatic cut and on direct stimulation in the curarized animal. Sodium phenanthrene-9-carboxylate did not produce this phenomenon in frogs, but instead elicited a morphine-like picture.

Of the novocaine-type acid derivatives (328, 329, table 9), the 3-isomer was less analgesic than the 9-isomer. This is the first instance observed in which this relationship existed and it is possible that here emetic action interfered with the development of other effects. The 9-derivative (329) showed more markedly the characteristic veratrine-like slow relaxation than any other 9-derivative; slight incoordination could be observed with doses as low as 25 mg

per kg. With all doses of No. 329 the effect on coordination was of brief duration.

The 3-methoxy-9-phenanthroic acid was not materially different from 3-methoxyphenanthrene or 9-phenanthroic acid, except that the phenomenon of delayed muscular relaxation was decidedly decreased by the entrance of the methoxyl group in position 3.

The octahydrophenanthroic acid (No. 202) was in all respects, including toxicity, more active than 9-phenanthroic acid. In particular the characteristic veratrine-like delayed relaxation was extremely marked.

β-(3-Phenanthryl)-propionic acid (No. 250, table 9), like the carboxylic acid series, was more effective in respect to analgesia, incoordination and emesis than the acid ester (No. 251) and the acid amide (No. 252), respectively. The amide was slightly more effective than the ester. In comparison with 3-phenanthroic acid the phenanthryl propionic acid was, except for emetic action, less effective, while the β-(3-phenanthryl) propionic acid amide (No. 252) was slightly more effective than 3-phenanthroic acid amide (No. 10).

2- and 3-Phenanthroic acid are very conveniently prepared by heating the corresponding acetylphenanthrenes with dilute aqueous sodium hypochlorite solution (*55*).

$$C_{14}H_9COCH_3 \xrightarrow{NaOCl} C_{14}H_9COOH$$

9-Phenanthroic acid is obtained by saponification of 9-cyanophenanthrene, which can be prepared readily by heating 9-bromophenanthrene with cuprous cyanide (*43*).

$$C_{14}H_{10} \longrightarrow C_{14}H_9Br \xrightarrow{CuCN} C_{14}H_9CN \longrightarrow C_{14}H_9COOH$$

The acid amide derivatives were prepared in the customary way by treating the acid chlorides with ammonia or dimethylamine (*55*).

$$C_{14}H_9COOH \xrightarrow{SOCl_2} C_{14}H_9COCl \begin{cases} NH_3 \longrightarrow C_{14}H_9CONH_2 \\ NH(CH_3)_2 \longrightarrow C_{14}H_9CON(CH_3)_2 \end{cases}$$

β-Diethylaminoethyl-3- and -9-phenanthroate hydrochloride were prepared by the action of β-diethylaminoethyl alcohol on the respective (3- and 9-) phenanthroyl chlorides (*42*).

$$C_{14}H_9COCl + HOCH_2CH_2N(C_2H_5)_2 \longrightarrow C_{14}H_9COOCH_2CH_2N(C_2H_5)_2HCl$$

3-Methoxy-9-phenanthroic acid was obtained by sodium hypochlorite oxidation of the corresponding methyl ketone (*60, 49*).

1, 2, 3, 4, 5, 6, 7, 8-Octahydro-9-phenanthroic acid was prepared by the Friedel-Crafts reaction with oxalyl chloride and sym.-octahydrophenanthrene (*25*).

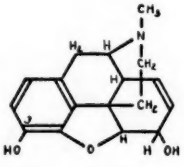
β-(2-Phenanthryl)- and β-(3-phenanthryl)-propionic acid were prepared by catalytic reduction of the corresponding β-(2-phenanthryl)- and β-(3-phenanthryl)-acrylic acid. The latter could be readily obtained by the action of malonic acid on the corresponding aldehydes (method of Perkin and of Robinson (*62*)) (*42*).

$$C_{14}H_9CHO \xrightarrow[\text{pyridine}]{CH_2(COOH)_2} C_{14}H_9CH{=}CHCOOH \xrightarrow[Pt]{H_2} C_{14}H_9CH_2CH_2COOH$$

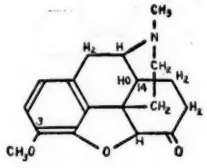
SUMMARY

Among the "simple" phenanthrene derivatives, the 3-derivatives, carrying in position 3, OH, NH_2, $COCH_3$, CH_2OH, $CHOHCH_3$, COOH, were in almost all respects more effective than the corresponding 2- and 9-derivatives; 3-hydroxyphenanthrene was also more effective than the corresponding 4- and 1-derivatives. It may be pointed out that the 3-derivatives, on the whole, have in comparison to the 2-derivatives but not to the 9-derivatives, lower melting points and a greater solubility in the common organic solvents.

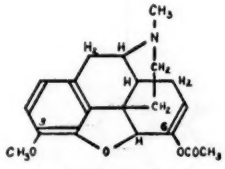
By alkylation or acetylation of the mono- and poly-hydroxyphenanthrenes (including morphenol) the effectiveness was decidedly decreased. The same relation held true with the carboxylic acids and their derivatives, esters, and amides. It is safe to assume that the methyl ethers and esters have a higher lipoid solubility than the free hydroxy or carboxylic acid derivatives. The higher activity of the latter, then, may be caused by their acid character. A similar relation in activity can be observed in the pair morphine-codeine. Practically all morphine derivatives within a useful range of activity contain a free phenolic hydroxyl in position 3. Noteworthy exceptions are Acedicon and Eukodal, both of which carry a methoxyl group in position 3. In these cases, it may be assumed that the acid character, within the base, which is apparently necessary for a certain grade of effectiveness, is guaranteed by the additional hydroxyl (position 14) in Eukodal and by the enolic acetoxyl (position 6) in Acedicon.



Morphine.



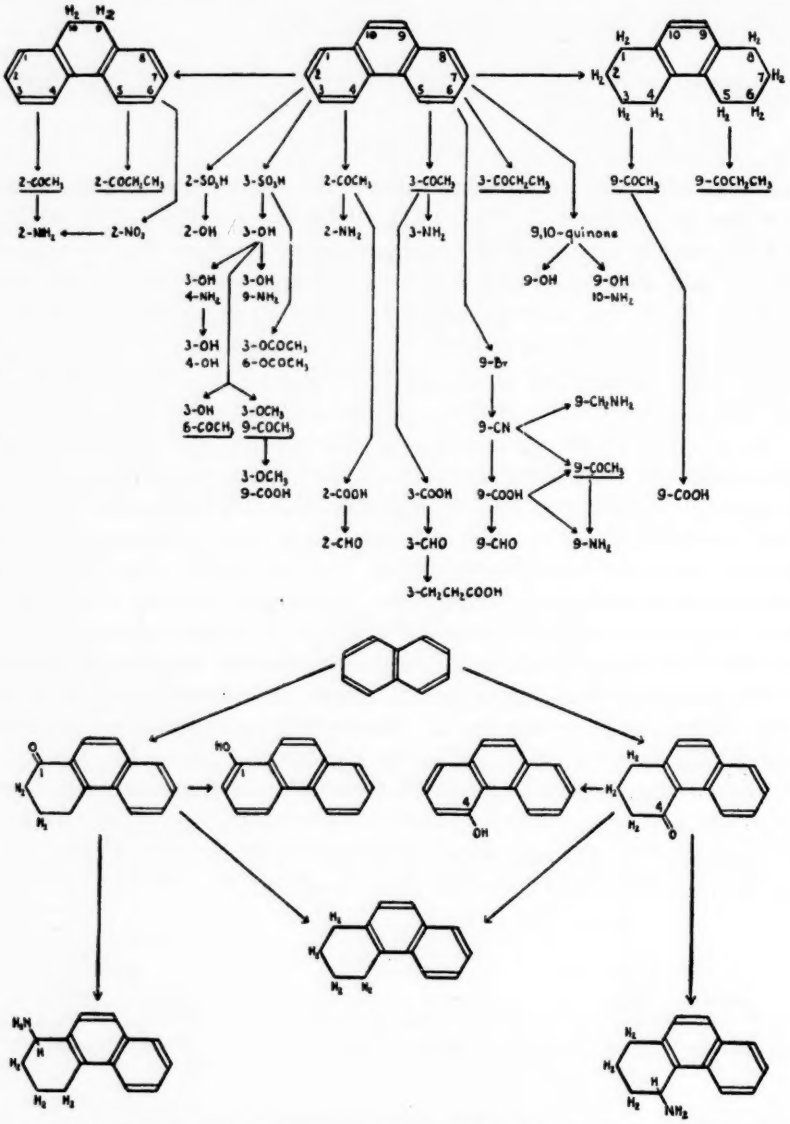
Dihydrohydroxycodeinone (Eucodal).



Acetyldemethylodihydrothebaine (Acedicon).

Methylation of the amino group (attached directly to the nucleus) decreased apparently uniformly the effectiveness. This is true with the phenanthrene derivatives, as well as with the corresponding 9, 10-dihydrophenanthrene derivatives and to some degree with the corresponding 1, 2, 3, 4-tetrahydrophenanthrene derivatives.

An interesting side action was seen, to a greater or less degree, with the majority of phenanthrene derivatives, carrying a substituent in position 9. This action consisted in a peculiar type of incoordination,



The compounds underlined serve as starting materials to the amino alcohols discussed in part 2.

characterized by veratrine-like delayed relaxation, and was particularly apparent in the derivatives of the 9-carboxylic acid, the most active among them being β-diethylaminoethyl-9-phenanthroate (No. 329).

No generalizations can be made as to the influence on pharmacological action of the entrance of another substituent in a given monosubstituted phenanthrene. The changes in pharmacological action are very likely dependent to some extent upon changes in chemical or physical properties, among others, differences in acidity or basicity, and in solubility. There was a decided increase in effectiveness from 3-hydroxyphenanthrene to 3, 4-dihydroxyphenanthrene, but at the same time, also, from 3-hydroxyphenanthrene to 3-hydroxy-4-aminophenanthrene. 3-Hydroxy-9-amino- and 9-hydroxy-10-aminophenanthrene were less effective, as could be expected on account of a mere neutralizing effect of the substituents, than the correlated monosubstituted compounds: 3-hydroxy-, 9-hydroxy-, and 9-amino-phenanthrene, respectively. The pharmacological data on the acetylphenanthrenes carrying an additional phenolic hydroxyl in the nucleus, equally, do not permit any conclusions. The decrease in "veratrine-like action" of the 9-phenanthroic acid by entrance of a methoxyl group in position 3 appears to be worth mentioning in this connection.

2. Amino Alcohol Derivatives of Phenanthrene and Hydrophenanthrenes

(a) AMINO KETONES ($-COCH_2NR_2$) AND AMINO ALCOHOLS OF THE ETHANOLAMINE TYPE ($-CHOHCH_2NR_2$)

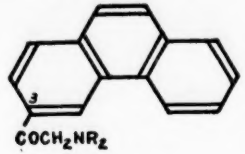


TABLE 10

A. AMINO KETONES

Position-substituent	Percent base	M. p., °C.	Solubility in water	Analgesia	Hours of duration*	General depression	Convulsions (cat)	Incoordination	Emesis	Rectal temperature	A. F. D.	M. C. D.
146 3-$COCH_2N(CH_3)_2$	87.8	228–230	s	M 100 Inj. M 100	5 5	M 50	N 200	M 50	200 (2) 77′	[a]100(−)1.5°	450	None
147 3-$COCH_2N(C_2H_5)_2$	88.9	231–232	s	M 150	−5	S 100	200 (2) 105′	S 150	150 (1) 34′ 200 (3) 53′	[b]100(−)0.7°	600	None
148 3-$COCH_2NC_4H_{10}$**	89.2	259–261	m. s	S 300	5	S 100	N 300	S 200	100 (1) 90′ 200 (1) 55′	[c]100(−)0.5°	----	----

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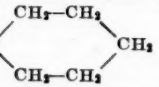
B. AMINO ALCOHOLS OF THE ETHANOLAMINE TYPE

Position-substituent	Percent base	M. p., ° C.	Solubility in water	Analgesia	Hours of duration*	General depression	Convulsions (cat)	Incoordination	Emesis	Rectal temperature	A. F. D.	M. C. D.
149 3-$CHOHCH_2N(CH_3)_2$	87.8	179.5–180.5	s	S 60	5	S 50	N 150	S 50	[d] 50 (3) 33′	[e] 50(−)0.6°	600	600
										100(−)1.1°		
150 3-$CHOHCH_2N(C_2H_5)_2$	88.9	163–164	s.	S 40	−5	[f] S 25	75 (2) 40′	S 25	[e] 50 (1) 34′	[h] 60(−)0.6°	600	150
				Inj. S 25	5+	S 20		S 20		20(−)0.5°		
325 3-$CHO(COCH_3)CH_2N(C_2H_5)_2$	90.2	221–221.5	m. s.	M 50	5+	S 75	N 75	S 40	N 75	25(+)0.5°	1,000	500
										75(−)0.4°		
151 3-$CHOHCH_2NC_5H_{10}$	89.3	242–243	m. s.	S 50	5	[f] S 40	[i] 100 (1) 51′	S 50	[j] 60 (1) 53′	[e] 100(−)1.5°	600	None
286 3-$CHOHCH_2NH_2$	86.7	235–236	s.	S 100	−5	S 60	N 100	N 100	[k] 60 (4) 36′	60(±)	350	None
				Inj. Mk 50	5+			S 25	20 (2) 30′	25(−)0.7°		
152 9-$CHOHCH_2N(CH_3)_2$	87.8	211–212	s.	M 150	5+	M 100	N 150	S 100	100 (3) 55′	100(−)1.6°	----	----

All of the data of this table refer to the hydrochlorides, in which form the substances were administered.

*Designated as more than (5+), less than (−5) or about (5) five hours, approximate estimate for the group.

**—NC_5H_{10}—



[e] The effect on temperature varied with the dose: With 50 mg the main effect was a brief initial rise with little or no secondary fall below the normal; with 100 mg the initial rise still occurred in 3 animals, but there was a distinct fall later; with 100 mg the fall was the main effect and with 200 mg it was the only effect noted.

[h] Initial rise was only occasional but the fall in temperature was delayed in its appearance as a rule to 2 to 5 hours after administration. It tended to appear earlier as the dose increased.

[i] Initial rise in temperature was frequent, in 2 animals with doses of 300 mg per kg. With this dose the secondary fall amounted to only 0.9°, average.

[d] Of 30 animals used, 50–150 mg per kg, 20 vomited, 3 others salivated and salivation after emesis was very profuse.

[i] Again brief initial rise in temperature was frequent.

[f] See text in regard to exciting effect with larger doses.

[j] Of 30 animals used only 7 vomited, 8 others salivated.

[k] Initial rise in temperature very frequent. With the injected doses, it was often the only effect, the average rise being 0.8° with 25 mg per kg.

[l] With 200 mg per kg 4 cats had convulsions and 1 died in 2 hours, the others recovered.

[m] Only 5 of 25 cats used (40 to 200 mg per kg) vomited; 2 others salivated.

[n] Of 15 animals used (60 to 100 mg per kg), all but 1 vomited, the emesis occurring earlier as the dose increased; of 15 animals receiving this substance by intramuscular injection 2 vomited with 20 mg, 4 with 25 mg (average 18′) but none vomited with 50 mg per kg.

Of this series (table 10 A and B) the most interesting and most striking in its effects is No. 150, (3-[2-(diethylamino)-1-hydroxy-ethyl] phenanthrene). The minimal effective analgesic dose was 40 or 38.5 mg per kg of base. One animal was definitely hyperirritable an hour after administration. With 50 mg the cats were quieter at first but two were excited at 5 hours. All trembled when handled and all developed a stiff-legged ataxic gait. With 60 mg the pupils were dilated and three cats were hyperactive. With 100 mg all of the cats were restless and excitable, the pupils were dilated and three animals had one or more convulsions but recovered. The dilated pupils, the restlessness, the stiff-legged, arched-back attitude, changing abruptly to violent squirming during the hyperirritability phase of the action of the drug gave an appearance very like that of morphinized cats. The heart rate was decreased, the respiratory rate increased, and the rectal temperature decreased, the last often after an initial rise. In mice, morphine-like turning and erection of the tail did not occur; in rabbits, doses of 20 and 40 mg per kg did not decrease respiratory activity, and doses up to 100 mg per kg in a Thiry-Vella loop dog did not definitely modify intestinal activity. The order of decreasing analgesic effectiveness of the three amino alcohols was diethylamino- (No. 150)→piperidino- (No. 151)→dimethylamino- (No. 149). The third member produced no excitement or convulsions; the second (No. 151) caused less excitement than No. 150, and was less convulsant.

The amino ketones, like the amino alcohols, increased the respiratory rate in the cat, but had relatively less effect on the heart rate. Both groups affected the body temperature in a similar manner. (See note 1, table 10, for typical effect.)

The veratrine-like delayed relaxation, characteristic of many of the 9-derivatives, was not seen with the 9-dimethylamino compound (No. 152). The effectiveness of the substance in comparison with the corresponding 3-derivative was definitely decreased.

If the alcoholic hydroxyl in the most active amino alcohol (No. 150) in this group was replaced or "muzzled" by acetylation, a product (No. 325) was obtained that had only slightly less analgesic action than No. 150, but was decidedly less emetic, less toxic, and less convulsant (for both cats and mice). The primary amino alcohol (No. 286) was less analgesic than any one of the three tertiary compounds (Nos. 149, 150, and 151), was apparently not convulsant, but it was very emetic and showed a greater degree of toxicity.

The effectiveness of the amino ketones (table 10 A) decreased in most respects in the order dimethylamino- (146)→diethylamino- (147)→piperidino- (148). They were, as a whole, less effective than the amino alcohols.

The tertiary amino ketones and amino alcohols were prepared by Mosettig and van de Kamp (63) from the corresponding acetylphenanthrenes as follows:

$$C_{14}H_9COCH_3 \xrightarrow{Br_2} C_{14}H_9COCH_2Br \xrightarrow{HNR_2} C_{14}H_9COCH_2NR_2$$

$$\xrightarrow[Pt]{H_2} C_{14}H_9CHOHCH_2NR_2 \qquad -NR_2 = -N(CH_3)_2,\ -N(C_2H_5)_2,\ -NC_5H_{10}$$

The primary amino ketones and alcohols had to be prepared by a different route (*42*):

$$C_{14}H_9COCH_3 \xrightarrow{C_5H_{11}ONO} C_{14}H_9COCH{:}NOH$$

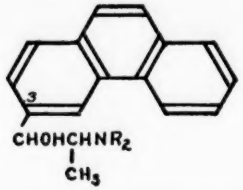
$$\xrightarrow{SnCl_2} C_{14}H_9COCH_2NH_2 \xrightarrow[Pt]{H_2} C_{14}H_9CHOHCH_2NH_2$$

The isonitrosoacetylphenanthrenes were obtained according to the method of Claisen and Manasse (*64*) by treating the corresponding acetylphenanthrenes with amyl nitrite and sodium alcoholate.

(b) AMINO ALCOHOLS OF PROPANOLAMINE TYPES

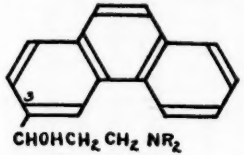
TABLE 11

A. AMINO ALCOHOLS OF THE β-PROPANOLAMINE TYPE (-CHOHCH(CH$_3$)NR$_2$)



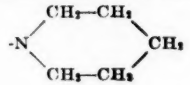
Position-substituent	Percent base	M. p., ° C	Solubility in water	Analgesia	Hours of duration	General depression	Convulsions (cat)	Incoordination	Emesis	Rectal temperature
287 3-CHOHCH(CH$_3$)N(CH$_3$)$_2$	88.4	240–242	s	S 60	5	S 60	N 75	N 75	75 (3) 16′	75 (±)
221 3-CHOHCH(CH$_3$)N(C$_2$H$_5$)$_2$	89.4	189–190	s [a]	[b] M 60	5+	M 60	75 (1) 120′	M 60	60 (4) 29′	60 (−) 0.6°
288 3-CHOHCH(CH$_3$)NHC$_2$H$_5$	88.4	256–257	s	M 75	5+	S 60	N 100	N 100	60 (2) 66′	100 (±)
220 3-CHOHCH(CH$_3$)NH$_2$	87.5	234–235	m. s	N 150		S 100	N 150	N 150	50 (3) 26′ 100 (5) 20′	150 (±)

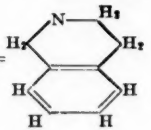
B. AMINO ALCOHOLS OF THE γ-PROPANOLAMINE TYPE (-CHOHCH$_2$CH$_2$NR$_2$)



352 3-CHOHCH$_2$CH$_2$N(C$_2$H$_5$)$_2$	89.4	138–140	2.5 gm in 100 cc	S 30	−5	S 30	40 (1) 60′	S 30	25 (2) 56′	50 (−) 0.9°
353 3-CHOHCH$_2$CH$_2$NC$_5$H$_{10}$*	87.7	185–185.5	0.06 gm in 100 cc	M 40	−5	S 30	40 (1) 42′	S 25	25 (3) 42′ 50 (5) 34′	40 (−) 0.8°
354 3-CHOHCH$_2$CH$_2$NC$_9$H$_{10}$**	91.0	208–208.5	[c]	N 200		S 100		S 100	100 (2) 64′ N 200	200 (±)

All of the data of this table refer to the hydrochlorides in which form the compounds were administered.

*-NC$_5$H$_{10}$= 

**-NC$_9$H$_{10}$= 

[a] Slight hydrolysis.

[b] With 60 mg per kg all of the cats were less quiet 2 hours after administration, 1 was restless on handling and all of them were easily excited; the pupils were dilated.

[c] At room temperature apparently no solution takes place. At 100° about 0.1 g dissolves in 100 cc water; the salt crystallizes from this solution on cooling.

In the "ephedrine type" series (287, 221, 288, 220, table 11A), there was only a slight difference, in analgesic action, between the dimethylamino and diethylamino compounds. Comparing the tertiary amino alcohol (221), the secondary (228), and the primary (220), there was only a slight difference between tertiary and secondary amine, but a great decrease in analgesic action from tertiary to primary amine. The primary showed the lowest depressant and the highest emetic action of the three. Compared to their lower analogs of the type -$CHOHCH_2.N<$, these propanolamines appeared decidedly less effective in most respects (compare the two tertiary amino alcohols 221 and 150 and the two primary alcohols 220 and 286).

In the propanolamines of the type -$CHOHCH_2CH_2.N<$ (352–354, table 11B), the diethylamino was slightly more analgesic and less convulsant and emetic than the piperidino compound. Contrast this with the very great decrease in activity observed with the tetrahydroisoquinolino compound (No. 354). Whether or not this great difference was due to the very low solubility of No. 354 or to some other effect of the basic group cannot be decided. Poor solubility alone seems an insufficient explanation in view of the great difference in solubility between Nos. 352 and 353 with little difference in physiological effect.

In comparison to their respective lower homologs, -$CHOHCH_2NR_2$, the diethylamino alcohol (352) and the piperidino alcohol (353) appeared more analgesic, more convulsant, and more emetic, but the margin between minimal analgesic dose and minimal convulsant or emetic dose was much less favorable than in the lower series.

It is known that compounds like adrenaline, ephedrine, and numerous analogs of the general β-phenylethylamine type exhibit the so-called sympathomimetic action in higher degree in contrast to similar derivatives that carry the nitrogen either closer to or further removed from the benzene nucleus. An analogous differentiation in activity between the phenanthrene derivative carrying the side chains -$CHOHCH_2NR_2$ and -$CHOHCH(CH_3)NR_2$ (N in β-position), on the one hand, and the chain -$CHOHCH_2CH_2NR_2$ (N in γ-position), on the other hand, could not be observed. The γ-series of compounds was relatively even more effective than the β-series in respect to analgesic and other effects. In neither of the series (β- or γ-) was vasoconstrictor activity noted; if any effect on the vasomotor mechanism was present it was rather vasodilator in character.

The "ephedrine analogs" in the phenanthrene series were prepared according to the scheme:

a. $C_{14}H_9COCH_2CH_3 \xrightarrow{Br_2} C_{14}H_9COCH(Br)CH_3 \xrightarrow{HNR_2}$

$C_{14}H_9COCH(CH_3)NR_2 \xrightarrow[Pt]{H_2} C_{14}H_9CHOHCH(CH_3)NR_2$

$-NR_2 = -NHC_2H_5, -N(CH_3)_2, -N(C_2H_5)_2$

b. $C_{14}H_9COCH_2CH_3 \xrightarrow{C_4H_9ONO} C_{14}H_9COCH(CH_3):NOH \xrightarrow[Pd]{H_2}$

$C_{14}H_9COCH(CH_3)NH_2 \xrightarrow[Pt]{H_2} C_{14}H_9CHOHCH(CH_3)NH_2$

In all instances only one form of the two possible diastereomeric racemic compounds was obtained by reduction of the respective amino ketones. A detailed description of the experiments concerned with these compounds and their analogs in the 2- and 9-series will appear elsewhere in a communication by Mosettig, Czerwin, and Krueger.

The amino alcohols of table 11B were obtained by catalytic reduction of the corresponding amino ketones, which were prepared by Mannich's method, as described by van de Kamp and Mosettig (*65*).

$C_{14}H_9COCH_3 \xrightarrow{CH_2O,\ HNR_2} C_{14}H_9COCH_2CH_2NR_2 \rightarrow C_{14}H_9CHOHCH_2CH_2NR_2$

$-NR_2 = -N(C_2H_5)_2, -NC_5H_{10}, -NC_9H_{10}$

(c) PHENOLIC AMINO ALCOHOLS

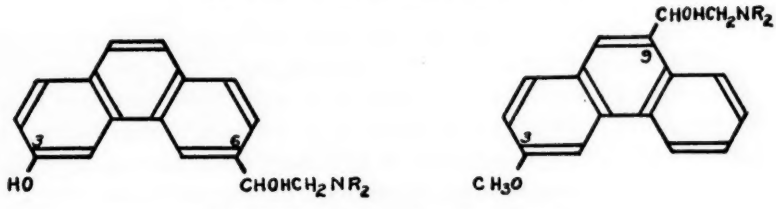


TABLE 12.—*Phenolic amino alcohols.*

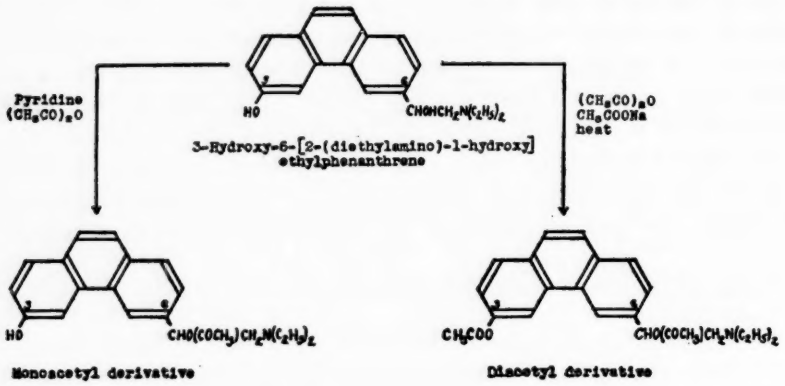
Position-substituent	Percent base	M. p., ° C.	Solubility in water	Analgesia	Hours of duration	General depression
255 {3-OH, 6-$CHOHCH_2N(C_2H_5)_2$}	89.4	186–187 dec.	v. s.	M 100	−5	S 50
256 {3-OH, 6-$CHO(COCH_3)CH_2N(C_2H_5)_2$}	90.6	198–200	m. s.	M 50	5+	S 40
284 {3-OCH_3, 9-$CHOHCH_2N(CH_3)_2$}	89.0	205–206	v. s.	M 90 Inj. S 50	5+ 5	S 75 S 40

Position-substituent	Percent base	Incoordination	Emesis	Rectal temperature	A. F. D.	M. C. D.
255 {3-OH, 6-$CHOHCH_2N(C_2H_5)_2$}	89.4	S 100	75 (3) 59′	75 (−) 0.5°	600	500
256 {3-OH, 6-$CHO(COCH_3)CH_2N(C_2H_5)_2$}	90.6	S 50	30 (1) 300′	20 (−) 0.5°	700	None
284 {3-OCH_3, 9-$CHOHCH_2N(CH_3)_2$}	89.0	S 75 S 40	75 (3) 36′ N 50	90 (−) 1.4°	------	------

All of the data of this table refer to the hydrochlorides in which form the substances were administered.

Number 255 (table 12) was synthesized for comparison with No. 150 (which is No. 255 minus the phenolic hydroxyl) in order to determine whether the augmenting effect exerted by the free phenolic hydroxyl in the morphine group would be likewise exhibited in the phenanthrene series. The result was disappointing, since in respect to analgesia No. 255 was less than half as effective as No. 150. The former, however, was less convulsant, although of the same order of toxicity. Also it did not produce the morphine-like excitement seen in cats with moderate doses of No. 150.

Acetylation (No. 256) of one of the hydroxyls (the alcoholic hydroxyl) of No. 255 restored the analgesic effectiveness about to the



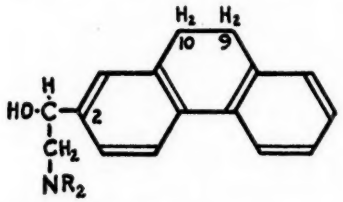
level of that of No. 150 without causing the appearance of exciting action, of increased toxicity, or of convulsions. Compare this with the augmenting effect of acetylation of the alcoholic hydroxyl in the morphine series. The introduction of a methoxyl group (No. 284 compared with 152) quite definitely increased effectiveness, especially analgesic action. Depressant and emetic effects were also increased.

The hydroxy (methoxy) amino alcohols were prepared by the procedure adopted by us for the preparation of the simple amino alcohols, starting from 3-hydroxy-6-acetylphenanthrene and 3-methoxy-9-acetylphenanthrene (*49*). The acetylation of 3-hydroxy-6-[2-(diethylamino)-1-hydroxy-ethyl]-phenanthrene yields, depending on the experimental conditions, either a monoacetyl or a diacetyl derivative (*22*).

(d) AMINO ALCOHOLS DERIVED FROM 9, 10-DIHYDROPHENANTHRENE

TABLE 13

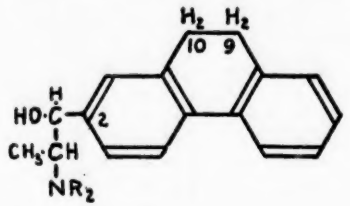
A. AMINO ALCOHOLS, ETHANOLAMINE TYPE, DERIVED FROM 9, 10-DIHYDROPHENANTHRENE



Position-substituent	Percent base	M. p., ° C.	Solubility grams in 100 cc H_2O	Analgesia	Hours of duration	General depression	Convulsions (Cat)	Incoordination	Emesis	Rectal temperature
340 2-CHOHCH$_2$N(CH$_3$)$_2$	88.0	170–171.5	3	M 40 Inj. M 25	5 5	S 40 S 25	N 100	S 30 S 20	25 (2) 50′ 20 (1) 54′	50 (+) 0.6° 100 (−) 0.8° 20 (+) 1.0°
341 2-CHO(COCH$_3$)CH$_2$N(CH$_3$)$_2$	89.4	216–217	5	M 30 Inj. S 25	5 −5	S 30 S 20	N 100	S 25 S 25	25 (3) 28′ N 25	25 (+) 0.7° 100 (−) 0.5° 20 (+) 1.5°
382 2-COCH$_2$N(C$_2$H$_5$)$_2$	88.9	173–176 dec.	10	S 50 Inj. S 30	5 5+	S 40 S 20	50 (2) 50′	S 45 S 20	45 (3) 32′ 20 (1) 14′	40 (+) 0.6° 50 (±) 0.6° 30 (+) 0.4°
342 2-CHOHCHN(C$_2$H$_5$)$_2$	89.0	184–186 dec.	3	M 25 Inj. S 10	5+ −5	S 15 S 10	20 (1) 28′	S 15 S 10	20 (1) 23′ 15 (1) 46′	20 (+) 0.6° 50 (−) 1.2° 10 (+) 0.3°
343 2-CHO(COCH$_2$)CH$_2$N(C$_2$H$_5$)$_2$	90.2	145–150	2	M 25 Inj. S 10	5 −5	S 20 S 10	25 (3) 33′	S 20 S 15	20 (1) 30′ 15 (1) 19′	20 (+) 0.7° 50 (−) 1.5° 15 (+) 0.7°
344 2-CHOHCH$_2$NC$_5$H$_{10}$*	89.4	241–242 vac., dec.	0.5	S 20 Inj. M 10	5 −5	S 20 S 7.5	25 (1) 60′	S 15 S 5	20 (1) 50′ 7.5 (1) 68′	15 (−) 0.5° 20 (±) 0.5° 7.5 (−) 0.6°
345 2-CHO(COCH$_3$)CH$_2$NC$_5$H$_{10}$*	90.5	213 dec.	10	M 20	−5	S 20	20 (1) 60′	S 15	15 (2) 28′	15 (−) 0.5°
346 2-CHOHCH$_2$NC$_5$H$_{10}$**	90.7	244–246 dec.	0.5	N 200	----------	S 200	----------	N 200	N 200	200 (−) 0.5°
347 2-CHO(COCH$_3$)CH$_2$NC$_5$H$_{10}$**	91.6	197–199 dec.	1	N 200	----------	S 200	----------	N 200	50 (1) 66′	200 (−) 0.4°

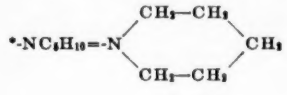
TABLE 13—Continued

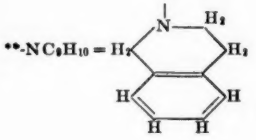
B. AMINO ALCOHOLS, PROPANOLAMINE TYPE, DERIVED FROM 9, 10-DIHYDROPHENANTHRENE



Position-substituent	Percent base	M. p., ° C.	Solubility grams in 100 cc H_2O	Analgesia	Hours of duration	General depression	Convulsions (Cat)	Incoordination	Emesis	Rectal temperature
348 2-CHOHCH(CH$_3$)N(C$_2$H$_5$)$_2$	89.4	209–210 dec.	0.38	S 30	5	S 25	20 (1) 69′	M 20	20 (2) 45′	50 (±)
349 2-CHOHCH(CH$_3$)NC$_5$H$_{10}$*	89.8	249–250	0.11	M 30	−5	S 25	20 (1) 62′	M 20	20 (4) 42′	50 (±)
350 2-CHOHCH(CH$_3$)NC$_9$H$_{10}$**	91.0	226–228	0.005	N 200		S 100		S 200	N 200	100 (−) 0.7°

The data in this table refer to the hydrochlorides in which form the compounds were administered.





Most of the members of this group surpassed in effectiveness the previously investigated amino alcohols which contain the alcoholic hydroxyl and amino group in the side chain. Unfortunately this high degree of activity concerned convulsant and emetic as well as analgesic and depressant effects; the minimal effective convulsant and emetic doses were as low or in some cases even lower than the minimal effective analgesic doses, and even in the absence of convulsions incoordination was marked. Whether these results were caused by the 9, 10-hydrogenation or by the shift of the amino alcohol side chain cannot be discussed, since at present neither 2-amino alcohols derived from non-hydrogenated phenanthrene, nor 3-amino alcohols derived from 9, 10-dihydrophenanthrene are available for comparison. The order of decreasing effectiveness of the members of group A (table 13), based upon their analgesic power, was $-NC_5H_{10}$, $-N(C_2H_5)_2$, $-N(CH_3)_2$. The diethylamino ketone (No. 382), in accordance with the previously described comparative effectiveness of amino alcohol-amino ketone, was only half as analgesic as the corresponding amino alcohol (No. 342) and also in other respects was less effective. The extremely low effectiveness of the tetrahydroisoquinolino compound (No. 346) was very striking. In this case it seems certain that the poor water-solubility, which is about the same as that of the piperidino compound (No. 344), cannot account for the low activity. Acetylation, surprisingly, in each of the four instances in this series, brought about practically no change in effectiveness.

The compounds of group A quickened the respiration moderately, frequently slowed the heart slightly, and quite uniformly brought about an initial rise in rectal temperature, whether or not convulsions occurred, which with the larger doses might be succeeded or sometimes replaced by a slight fall. The high degree of analgesic action with the more soluble compounds which could be given by intramuscular injection, is also noteworthy. With the dimethylamino and diethylamino derivatives a slight degree of exciting effect was noted with doses at or near the convulsant level. This manifested itself principally in signs of terror and resistance to handling; except for actual convulsive movements, the animals were mostly quiet in their cages.

The three members of group B (table 13) were in all respects very similar to the corresponding members of group A. Again the tetrahydroisoquinolino compound was very inactive. In this case water-insolubility was very unfavorable. The diethylamino and piperidino compounds (Nos. 348 and 349) were slightly less analgesic than their lower homologs (Nos. 342 and 344), but exhibited equally great convulsant and emetic effects.

The amino alcohols listed in tables 13A and 13B were prepared from 9, 10-dihydro-2-acetylphenanthrene in essentially the same way

as their nonhydrogenated analogs as described by Burger and Mosettig (*21*).

$$C_{14}H_{11}COCH_3 \rightarrow C_{14}H_{11}COCH_2Br \rightarrow C_{14}H_{11}COCH_2NR_2 \rightarrow C_{14}H_{11}CHOHCH_2NR_2 \rightarrow C_{14}H_{11}CHO(COCH_3)CH_2NR_2$$

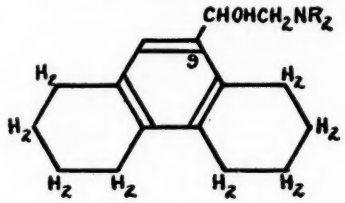
$$C_{14}H_{11}COCH_2CH_3 \rightarrow C_{14}H_{11}COCHBrCH_3 \rightarrow C_{14}H_{11}COCH(CH_3)NR_2 \rightarrow C_{14}H_{11}CHOHCH(CH_3)NR_2 \rightarrow C_{14}H_{11}CHO(COCH_3)CH(CH_3)NR_2$$

$$-NR_2 = -N(CH_3)_2,\ -N(C_2H_5)_2,\ -NC_5H_{10},\ -NC_9H_{10}$$

(e) AMINO ALCOHOLS DERIVED FROM SYMMETRIC OCTAHYDROPHENANTHRENE

TABLE 14.—*Amino alcohols derived from octahydrophenanthrene*

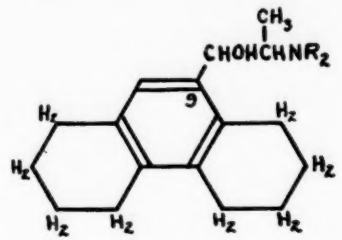
A. ETHANOLAMINE TYPE



Position-substituent	Percent base	M. p., ° C.	Solubility in water	Analgesia	Hours of duration	General depression	Incoordination	Emesis	Rectal temperature
263 9-$CHOHCH_2N(CH_3)_2$	88.2	217–218	v. s.	N 200 Inj. S 50	5	S 100 S 25	N 200 S 25	100 (4) 12′ 50 (1) 13′	200 (±)
278 9-$CHOHCH_2N(C_2H_5)_2$	89.2	148–149	v. s.	N 100 Inj. S 25	brief.	S 50 S 25	S 50 S 25	50 (3) 50′ 100 (5) 19′ 25 (1) 60′	100 (−) 0.6° 25 (+) 0.8°
279 9-$CHOHCH_2NC_5H_{10}$*	89.6	227–228	m. s.	N 100 Inj. N 25	--- ---	S 50 S 25	N 100 S 25	50 (3) 19′ 25 (1) 55′	50 (−) 0.8° 25 (±)

TABLE 14.—*Amino alcohols derived from octahydrophenanthrene*—Continued

B. PROPANOLAMINE TYPE



Position-substituent	Percent base	M. p., ° C.	Solubility in water	Analgesia	Hours of duration	General depression	Incoordination	Emesis	Rectal temperature
282 9-CHOHCH(CH3)NHCH3	88.2	218–219	v. s	S 100 Inj. N 25	5	S 50 S 25	N 100 N 25	50 (1) 17′ N 25	100 (±) 25 (+) 1.1°
280 9-CHOHCH(CH3)N(CH3)2	88.7	228–229	s	M 75	5	• S 50	S 50	50 (2) 71′ 100 (5) 70′	100 (+) 0.8°
283 9-CHOHCH(CH3)NHC2H5	88.7	118–119	v. s	N 100 Inj. N 25	---------- ----------	S 50 S 25	S 100 N 25	50 (2) 14′ 100 (2) 7′ 25 (1) 61′	100 (±) 25 (+) 1.2°
281 9-CHOHCH(CH3)NC5H10*	90.0	235–236	s	N 100	----------	S 50	S 75	75 (4) 70′ 100 (2) 50′	100 (−) 0.9°

All of the data of this table refer to the hydrochlorides in which form the substances were administered.

*-NC_5H_{10}=-N(CH2—CH2, CH2—CH2, CH2)

• 1 animal of 5 died within 5 hours with a dose of 100 mg per kg.

Early vomiting was characteristic of members of group A, table 14, when the substances were administered orally, probably in part at least due to local irritation, and occurring often before there was time for complete absorption. Therefore, development of full effect with oral doses could not be observed and caution must be exercised in making comparisons. With the few intramuscular doses that were given, the incidence of vomiting was less. Tentatively the substances may be placed in the order of decreasing analgesic effectiveness, diethylamino- (278), dimethylamino- (263), piperidino- (279). The emetic action of the three was practically the same. If comparison is made of the effect of oral doses, the octahydro-9-dimethylamino alcohol (No. 263) would seem to be less analgesic than the nonhydrogenated 9-dimethylamino alcohol (No. 152); but on account of the high emetic action of the octahydro derivative it is doubtful if this is the true relation.

The amino alcohols of group B (table 14) were a little less emetic and perhaps on this account more analgesic action was observed with oral doses. The two secondary amino alcohols (Nos. 282 and 283) were apparently less analgesic than the tertiary amino alcohol (No. 280). Also the piperidino alcohol (No. 281) was less effective than the dimethylamino (No. 280), although the latter was the more emetic.

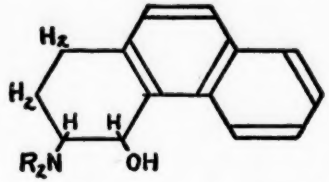
The amino alcohols in table 14A were prepared from 9-acetyl-1, 2, 3, 4, 5, 6, 7, 8-octahydrophenanthrene essentially in the same way as their nonhydrogenated analogs from 3-acetylphenanthrene (*25*).

$$C_{14}H_{17}COCH_3 \xrightarrow{3\ \text{steps}} C_{14}H_{17}CHOHCH_2NR_2$$

$$C_{14}H_{17}COCH_2CH_3 \xrightarrow{3\ \text{steps}} C_{14}H_{17}CHOHCH(CH_3)NR_2$$

$$-NR_2 = -NHCH_3,\ -NHC_2H_5,\ -N(CH_3)_2,\ -N(C_2H_5)_2,\ -NC_5H_{10}$$

(f) CYCLIC AMINO ALCOHOLS DERIVED FROM TETRAHYDROPHENANTHRENE



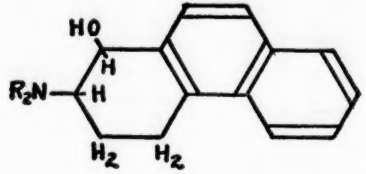
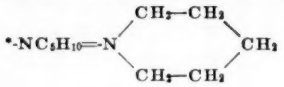
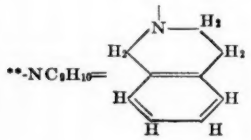


TABLE 15.—*Cyclic amino alcohols derived from tetrahydrophenanthrene*

Position-substituent	Percent base	M. p., ° C.	Solubility in water	Analgesia	Hours of duration	General depression	Convulsions (cat)	Incoordination	Emesis	Rectal temperature	A.F.D.	M.C.D.
257 {3-N(CH3)2 / 4-OH}	86.9	230	v. s	M 60	5+	S 50	60 (1) 69′ 80 (3) 55′	S 50	[a] 50 (3) 33′	[b] 50 (−)1.4°	350	300
309 {3-N(C2H5)2 / 4-OH}	88.1	239–240	3.0 g in 100 cc	M 40	5+	S 30	N 50	S 30	[c] 30 (3) 33′	40 (−)0.5°	----	----
258 {3-NC5H10* / 4-OH}	88.5	245	s	M 40	5+	S 20	[d] 40 (1) 47′	S 25	[e] 20 (1) 75′	30 (+) 0.7°	270	170
259 {3-NC9H10** / 4-OH}	90.0	232	0.6 g in 100 cc	S 15	5+	S 15	50 (1) 35′	S 15	(f)	[g] 10 (+)0.8°	400	270
351 {3-NC9H10** / 4-OCOCH3}	91.1	200–201 dec	0.025 g in 100 cc	N 300	----	S 300	----	N 300	300 (1) 11′	300 (+)0.5°	----	----
260 {2-N (CH3)2 / 1-OH}	86.9	223–224	v. s	S 40	−5	S 40	100 (1)48′	S 40	[h] 40 (4) 42′	50 (+)0.5°	375	250
261 {2-NC5H10* / 1-OH}	88.5	258–260	s.[i]	S 20	5	S 20	[j] 100 (3) 58′	S 20	[k] 15 (1) 110′	60 (+)0.7°	270	200
262 {2-NC9H10** / 1-OH}	90.0	226 dec	s.[i]	S 50	5	S 30	N 100	S 50	[l] 60 (1) 53′	50 (+)0.7°	550	330

The data refer to the hydrochlorides in which form these substances were administered.





[a] Of 18 animals used, 50 to 100 mg per kg, 11 vomited.
[b] With larger doses, a rise in temperature (0.8° with 100 mg per kg) predominated, probably an accompaniment of the convulsant action.
[c] Of 15 animals used, 30 to 50 mg per kg, 8 vomited.
[d] 2 of 3 animals with 100 mg per kg had convulsions and died within an hour.
[e] Of 28 animals used, 20 to 100 mg per kg, only 5 vomited; profuse salivation in 9 others.
[f] No vomiting. Of the 36 animals used, 10 to 150 mg per kg, 12 salivated, salivation being most frequent with doses of 50 to 100 mg.
[g] A rise in temperature was almost invariable, still being in evidence 5 hours after administration.
[h] Of 18 animals used, 40 to 100 mg per kg, 11 vomited.
[i] Hydrolyzes weakly.
[j] 2 of 3 animals with 100 mg per kg died within 4 hours.
[k] Of 26 animals used, 15 to 100 mg per kg, 6 vomited, 5 others salivated.
[l] Of 28 animals used, 30 to 100 mg per kg, only 2 vomited, 5 others salivated with 70 and 100 mg per kg.

4192°—38——7

Among the cyclic amino alcohols of table 15 there are three pairs of isomers, a 2, 1-series and a 3, 4-series, but the relationships within a series or between the series are not entirely regular. The group as a whole possessed considerable analgesic power but were convulsant and quite emetic. The margin between analgesic and convulsant doses was wider in the 2, 1-series. The compounds may be arranged in order of decreasing effectiveness according to substituents as follows:

Order of decreasing effectiveness

Analgesia	Convulsions	Toxicity	Emesis
	3, 4-series		
$-NC_9H_{10}$	$-NC_5H_{10}$	$-NC_5H_{10}$	$-N(CH_3)_2$ and
$-NC_5H_{10}$ and	$-NC_9H_{10}$	$-N(CH_3)_2$	$-N(C_2H_5)_2$
$-N(C_2H_5)_2$	$-N(CH_3)_2$	$-NC_9H_{10}$	$-NC_5H_{10}$
$-N(CH_3)_2$	$-N(C_2H_5)_2$		$-NC_9H_{10}$
	2, 1-series		
$-NC_5H_{10}$	$-N(CH_3)_2$	$-NC_5H_{10}$	$-N(CH_3)_2$
$-N(CH_3)_2$	$-NC_5H_{10}$	$-N(CH_3)_2$	$-NC_5H_{10}$
$-NC_9H_{10}$	$-NC_9H_{10}$	$-NC_9H_{10}$	$-NC_9H_{10}$

Changes in heart rate were not marked when these substances were administered, but a slight to moderate quickening was not infrequent. The respiratory rate was almost invariably increased, sometimes very greatly. An initial rise in temperature was very frequent, being most uniform and most persistent with No. 259. Often with the other substances a slight secondary fall was noted.

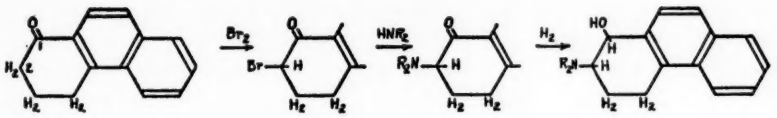
An interesting effect on the isolated frog's heart, exhibited to a very high degree with No. 259 and to a lesser degree with other members of the group, has been observed (*66*). This consisted in an effect on conduction, amounting to a complete blocking of ventricular contraction, and obtainable with a dilution of No. 259 as high as 1: 500,000 (Straub heart perfusion method). So far a similar effect on the mammalian heart has not been obtained. The study of the phenomenon is being continued to determine the conditions under which it may be obtained and its mechanism.

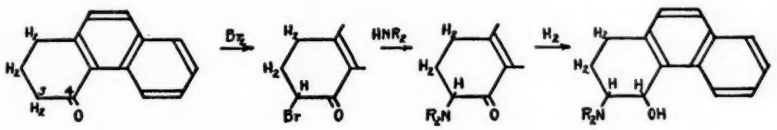
It is noteworthy that among these cyclic amino alcohols as compared with the "straight chain" series (table 13), the tetrahydroisoquinolino derivatives showed a high degree of activity.

The acetyl product, No. 351, was prepared in order to study the influence of "muzzling" the alcoholic hydroxyl. It is, however, only sparingly soluble and the results must be interpreted with caution.

The amino alcohols listed in table 15 were prepared according to Mosettig and Burger (*67*), starting from 1-keto- and 4-keto-1, 2, 3, 4-tetrahydrophenanthrene, respectively. By bromination, the bro-

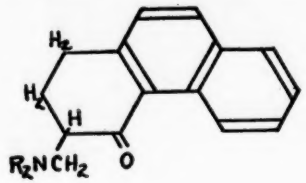
mine enters in the α-position to the carbonyl group, and is then exchanged with a tertiary amino group. The resulting amino ketones are finally reduced catalytically to the corresponding amino alcohols. Although in this procedure the formation of two diastereomeric forms can be expected, actually in all the cases only one form is produced.

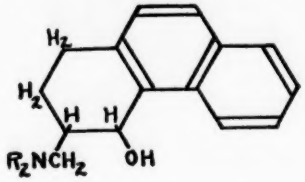


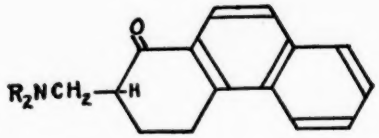


$-NR_2 = -N(CH_3)_2, -N(C_2H_5)_2, -NC_5H_{10}, -NC_9H_{10}$

(g) HOMOLOGOUS CYCLIC AMINO ALCOHOLS DERIVED FROM TETRAHYDROPHENANTHRENE







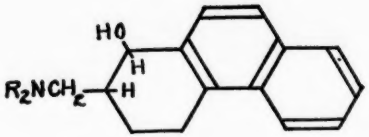
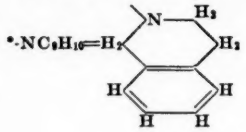
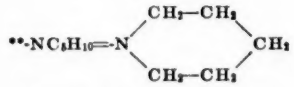


TABLE 16.—*Homologous cyclic amino alcohols derived from tetrahydrophenanthrene*

	Position-substituent	Percent base	M. p., °C.	Solubility grams in 100 cc water	Analgesia	Hours of duration	General depression	Convulsions (cat)	Incoordination	Emesis	Rectal temperature
383	3-$CH_2N(C_2H_5)_2$ 4-O	88.5	151–153	12.5	S 50	5	S 50	75 (3) 36′	50	40 (3) 46′	50 (+) 0.7° 100 (−) 0.5°
384	3-$CH_2N(C_2H_5)_2$ 4-OH	88.6	173–174	6.6	S 25	−5	S 25	• 40 (2) 60′	S 15 M 30	15 (2) 28′ 20 (2) 33′	20 (+) 0.3° 40 (−) 0.8°
407	3-$CH_2NC_5H_{10}$• 4-OH	90.4	183–184	[b] 0.6	Inj. S 15 S 40	−5 5+	S 10 [c] N 50	N 100	N 50	Sal 50 (2) 60′	10 (+) 0.6° 25 (+) 0.8°
385	2-$CH_2NC_5H_{10}$•• 1-O	88.9	170–220 dec.	10.0	S 25	Brief	S 30	50 (3) 25′	S 30	20 (1) 49′	20 (±) 40 (−) 0.5°
386	2-$CH_2NC_5H_{10}$•• 1-OH	89.0	240–241 dec.	2.0	S 25	−5	S 20	30 (1) 69′	S 20	20 (4) 55′	20 (+) 0.7° 50 (±)

All of the data in this table refer to the hydrochlorides in which form the substances were administered.





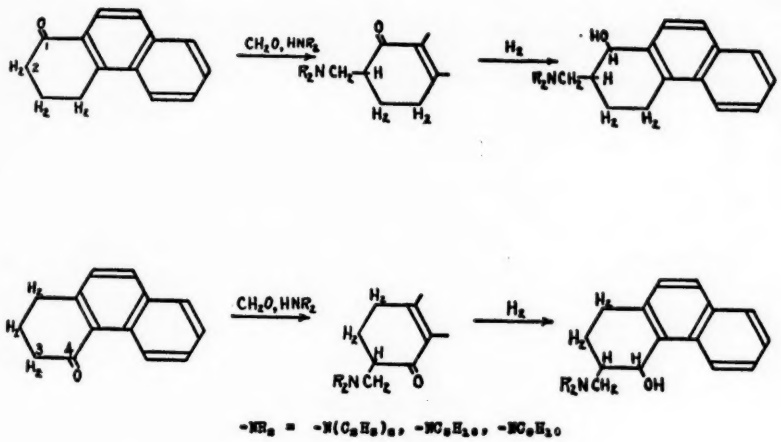
(•) With 50 mg per kg each of 5 animals had convulsions, average 40′, and 1 died within 2 hours; the others recovered rapidly and were nearly normal in 5 hours.
(b) Hydrolyzes slightly.
(c) No quieting effect observed; typical morphine-like excitement, 25 mg per kg and above (see text).

The amino alcohols of table 16 for the most part produced a picture qualitatively like that of their lower homologs (table 15), but a uniform quantitative relationship between the corresponding members of the two groups could not be established. For example, the higher piperidino compound (No. 386 of table 16) had about the same analgesic action but was more convulsant than its lower homolog (No. 261 of table 15); the higher diethylamino alcohol (No. 384 of table 16) was more analgesic, more convulsant, and more emetic than No. 309 of table 15; but the higher tetrahydroisoquinolino alcohol (No. 407 of table 16) was less analgesic, convulsant, and emetic than No. 259 (table 15). The duration of action was briefer with the higher homologs.

In accordance with previous experience, the diethylamino ketone (No. 383) was less analgesic and depressant, less convulsant, and probably less toxic than the corresponding amino alcohol (No. 384). The piperidino ketone (No. 385) was hardly less analgesic except in duration of action, but was less depressant and less convulsant than the corresponding piperidino alcohol (No. 386).

The tetrahydroisoquinolino compound (No. 407) is the most interesting member of the series. With a dose as small as 25 mg per kg three of five animals showed the rubbing and rolling ("pleasure signs") characteristic with small doses of morphine and its derivatives. With 40 mg per kg all of the cats showed morphine-like restlessness, exaggerated when the animals were handled. With 75 mg per kg the picture was indistinguishable from that produced by morphine—motor excitement, jerky purposeless movements, dilated pupils, increased heart rate, increased temperature, and moderate analgesia. Even with 100 mg per kg there was no apparent increase in reflexes and no convulsant action. It will be remembered that the lower homolog (No. 259) did not produce morphine-like excitement but was convulsant with three times its analgesic dose. Neither substance caused vomiting; salivation occurred more frequently with No. 259.

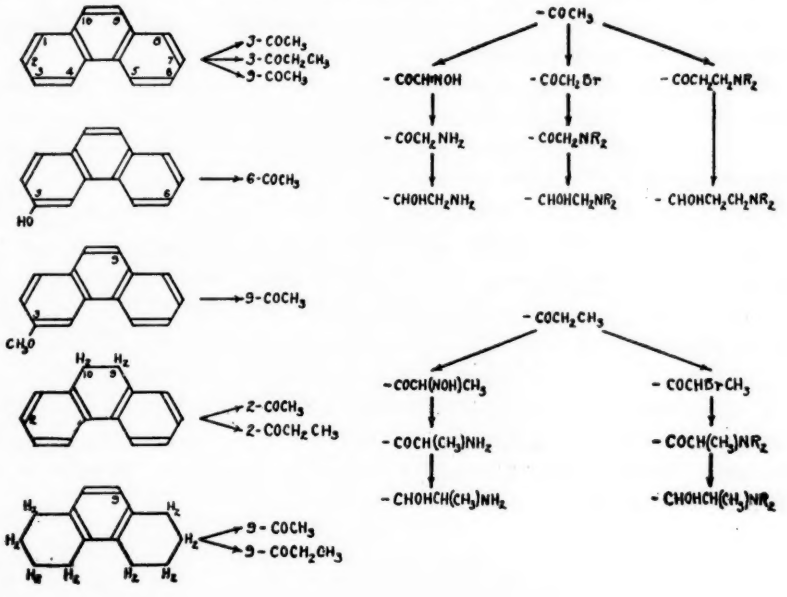
The amino ketones and amino alcohols listed in table 16 were prepared by the application of the "Mannich amino ketone synthesis" to 1-keto- and 4-keto-tetrahydrophenanthrene, respectively (*48*). Also in this series, only one of the two possible diastereomeric racemic amino alcohols is formed in the catalytic reduction of the corresponding ketones.

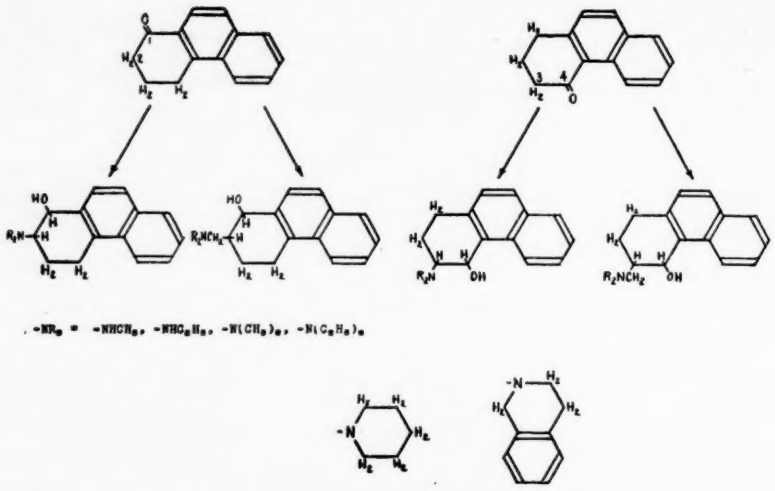


SUMMARY

In the group of amino alcohols carrying the nitrogen and the alcoholic hydroxyl in a side chain the diethylamino alcohols showed, generally, the highest analgesic and depressant action; the dimethylamino derivative was least active and the piperidino compounds were usually intermediate; the last were often the most toxic. Comparatively, the py-tetrahydroisoquinolino derivatives were exceedingly low in analgesic action.

Schematic review of the preparation of the principal compounds of Part II.





The propanolamines of the type -CHOHCH(CH_3)NR_2 were, generally, less active than the lower homologs, -CHOHCH_2NR_2, and the latter were less active than the propanolamines of the type -CHOH-$CH_2CH_2NR_2$.

In the few cases available for comparison the primary amino alcohols were decidedly less effective than the tertiary alcohols, but were more emetic. No definite conclusion could be drawn as to the effect of introducing a phenolic hydroxyl group into the phenanthrene nucleus of these amino alcohols. The amino alcohols derived from 9, 10-dihydrophenanthrene were, with the exception of the tetrahydroisoquinolino derivatives, highly analgesic but at the same time they were very convulsant.

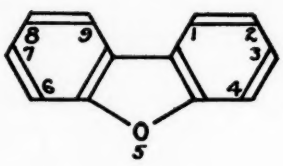
The amino alcohols derived from sym.-octahydrophenanthrene appeared to be locally irritant, since vomiting occurred very soon after oral administration. This interfered with correct evaluation of their activity.

Relatively the most powerful synthetic analgesics were found among the so-called "cyclic amino alcohols," grouped in tables 15 and 16. It should be noted that here the isoquinolino derivatives, in contrast with the isoquinolino alcohols carrying the basic group and the alcoholic group in a side chain, showed an activity equal to, or higher than, that of the other members of their respective groups.

It is perhaps of special interest that one of these isoquinolino compounds (No. 407) produced in the cat a very typical morphine-like picture without evidence of any convulsant action and almost without any emetic effect.

3. Derivatives of Other Condensed Ring Systems

(a) DIBENZOFURAN, TETRAHYDRODIBENZOFURAN, AND SIMPLE AMINO, CARBONYL, AND CARBOXYL DERIVATIVES



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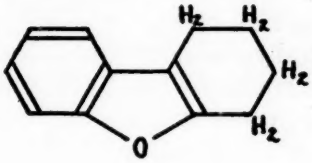


334

TABLE 17.—*Dibenzofuran, tetrahydrodibenzofuran, and simple amino, carbonyl, and carboxyl derivatives*

Position-substituent	M. p., °C.	Solubility in olive oil*	Analgesia	Hours of duration	General depression	Incoordination	Emesis	Rectal temperature
189 Dibenzofuran	84–85	s	N 500		S 300	S 500	N 500	500 (−) 0.7°
334 1, 2, 3, 4-tetrahydro-	oil	v. s.	N 300		S 200	S 300	N 300	300 (−) 0.6°
190 3-NH_2 [a]	98	v. s.	M 40	5+	[b] M 25	S 25	25 (3) 100′	25 (−) 2.4°
333 3-$N(CH_3)_2$ [c]	191–193		S 40	−5	S 30	S 40	40 (1) 40′	40 (−) 0.7°
191 2-$COCH_3$	80	s	N 300		S 100	S 300	100 (1) 286′	100 (−) 0.6°
228 2-$COCH_2CH_3$	100–101	s	S 400	−5	S 200	N 400	N 400	400 (−) 0.5°
229 2-$CHOHCH_3$	63–64	s	S 200	5+	[d] S 200	S 200	300 (1) 103′	300 (−) 1.0°
335 7-$COCH_3$ 1, 2, 3, 4-tetrahydro-	67–68. 5	v. s.	M 300	5+	S 200	S 300	N 300	300 (−) 0.5°
289 2-COONa [e]			M 200	5+	M 200	M 200	Sal 200 (2) 60′	200 (±)
290 2-$COOCH_3$	83–84	s	N 300		S 200	S 200	N 300	200 (−) 0.6°

*All (except 333 and 289) practically insoluble in water.
[a] The hydrochloride is only sparingly soluble in water, hydrolyzes. Administered as base.
[b] With 100 mg per kg 3 of 5 animals died within 5 hours, a fourth animal died the next morning.
[c] Data refer to hydrochloride (85.2 percent base) in which form the substance was administered. Solubility 1.2 parts per 100 cc of water.
[d] All animals to which this substance was administered (200 and 300 mg per kg) died, 1 within 24 hours, the others within 72 hours, strongly suggesting a delayed toxic action, since the effect during the first few hours after administration was not unusually pronounced.
[e] Easily soluble in water.

Dibenzofuran behaved pharmacologically similarly to phenanthrene, but caused less muscular disturbance and less decrease in temperature (table 17). Like phenanthrene it had no analgesic effect. The tetrahydro compound (No. 334) was slightly more effective than the non-hydrogenated derivative (No. 189). The 3-aminodibenzofuran (No. 190) was in every respect, but especially in action on temperature and emesis, more effective than 3-aminophenanthrene (table 4). The 3-dimethylaminodibenzofuran (No. 333) was less analgesic, less depressant, and less emetic than the primary compound (No. 190); a parallel drop in activity from the amino to the dimethylamino compound was observed in the phenanthrene series also. 2-Acetyldibenzofuran (No. 191) was similar to 3-acetylphenanthrene (table 7), but, as in the phenanthrene series, the effect increased slightly from 2-acetyldibenzofuran to 2-propionyldibenzofuran (No. 228). The 2-dibenzofuran methyl carbinol (No. 229) was more analgesic than

any of the three isomeric (2-, 3-, 9-) methyl carbinols, in the phenanthrene series, but was at the same time also more toxic. (See footnote *d*, table 17.) On the other hand, the free dibenzofuran carboxylic acid was less analgesic than phenanthrene-3-carboxylic acid, but in both series analgesic activity was decreased by esterification. Acetyltetrahydrodibenzofuran (No. 335) was definitely more analgesic than the analogous non-hydrogenated compound.

In comparing dibenzofuran and phenanthrene derivatives it should be remembered that in the former series position isomers have not yet been studied, so that we do not know whether a difference exists in this respect as with the phenanthrenes, or whether the particular dibenzofuran studied is the most effective among its possible isomers.

The *dibenzofuran* used for this purpose was obtained by distilling over sodium a dibenzofuran (m. p. 82–84°) purchased as "diphenylene oxide, pure" from Gesellschaft für Teerverwertung, Duisburg-Meiderich.

1, 2, 3, 4-Tetrahydrodibenzofuran was prepared by reduction of dibenzofuran with sodium and cyclohexanol (*68, 69*). For catalytic reduction see Cullinane and Padfield (*70*).

3-Aminodibenzofuran was obtained by reduction of the corresponding nitro derivative, according to Borsche and Bothe (*71, 72*). The numbering of dibenzofuran is in discrepancy with that used in previous and current literature, and therefore also in discrepancy with the numbering of the analogous carbazole. (See footnote 5 in the paper by Mosettig and Robinson (*72*).)

3-Dimethylaminodibenzofuran was prepared by methylation of the primary amine with methyl iodide and sodium acetate. Kirkpatrick and Parker (*73*) quote for the hydrochloride, m. p. 230–232°, and for the free base m. p. 96°, while the respective melting points found by us are 191–193° and 99–100°.

2-Acetyldibenzofuran and 2-propionyldibenzofuran were prepared by the method of Friedel and Crafts (*74, 75, 76*).

2-Dibenzofuryl methyl carbinol was prepared by catalytic reduction of 2-acetyldibenzofuran (absolute alcohol, platinum oxide) (*76*).

1, 2, 3, 4-Tetrahydro-7-acetyldibenzofuran was prepared by the Friedel-Crafts reaction on 1, 2, 3, 4-tetrahydrodibenzofuran (*77*).

(b)[•] AMINO KETONES AND AMINO ALCOHOLS DERIVED FROM DIBENZOFURAN

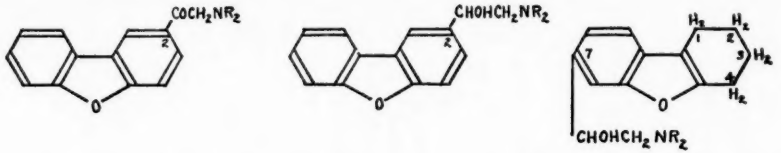
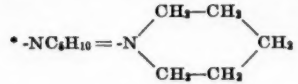


TABLE 18.—*Amino ketones and amino alcohols derived from dibenzofuran*

	Position-substituent	Per-cent base	M. p., ° C	Solubility in water	Analgesia	Hours of duration	General depression	Convulsions (cat)	Incoordination	Emesis	Rectal temperature	A. F. D.	M. C. D.
192	2-$COCH_2N(CH_3)_2$	87.4	235–237 dec.	s	S 75	−5	S 50	N 100	S 50	50 (2) 28′	60 (−) 0.8°	450	450
193	2-$CHOHCH_2N(CH_3)_2$	87.5	173–174	s	S 50	−5	M 40	N 100	S 40	40 (1) 31′	50 (−) 0.5°	550	500
291	2-$COCH_2N(C_2H_5)_2$	88.5	200–211 dec.	v. s	S 60	−5	M 75	75 (1) 60′	M 75	75 (2) 75′	50 (−) 0.8°	475	400
292	2-$CHOHCH_2N(C_2H_5)_2$	88.6	157–159.5	v. s	S 30	5+	S 25	100 (2) 45′	S 50	25 (1) 84′	25 (+) 0.6°	300	70
194	2-$CHOHCH_2NC_5H_{10}$[•]	89.0	245–251	m. s	M 60	5+	S 50	60 (2) 40′	M 60	60 (3) 52′	60 (±) 0.5°	325	200
311	2-$CHOHCH_2NHC_2H_5$	87.5	218–219.5	2 g in 100 cc	M 60	5+	S 50	N 75	S 50	50 (2) 45′	50 (−) 1.1°	------	------
310	2-$CHOHCH_2NH_2$	86.2	261	0.6 g in 100 cc	• S 75	5+	S 40	N 75	S 50	40 (4) 35′	40 (−) 1.0°	375	None
336	{7-$CHOHCH_2N(CH_3)_2$ {1, 2, 3, 4-tetrahydro	87.7	218–220	41 g in 100 cc	S 40	5	S 40	N 60	S 40	40 (3) 28′	60 (−) 0.7°	------	------

All of the data in this table refer to the hydrochlorides in which form the substances were administered.



• Possibly the emetic effect interfered with full development of effectiveness.

The pharmacological results with this group (table 18), particularly in regard to analgesic effectiveness, may be summarized as follows: The amino ketones, the dimethylamino- (192) and the diethylamino- (291), were less effective than the corresponding amino alcohols (193 and 292). The effectiveness in the series of the tertiary amino alcohols decreased in the order diethylamino- (292)→ dimethylamino- (193)→ piperidino- alcohol (194), and decreased, as was to be expected, from the tertiary diethylamino alcohol (292) through the secondary ethylamino alcohol (311) to the primary amino alcohol (310).

Hydrogenation (336) seemed not to bring about any particular increase in effectiveness, but since the two compounds compared (336 and 193) carry the alkamine side chain in different nuclear positions, a definite conclusion cannot be drawn.

The piperidino alcohol (194) was apparently the most convulsant (in cats), the primary amino alcohol (310) the most emetic, which facts are also in accordance with the results with analogous compounds in the phenanthrene series. If one compares corresponding amino alcohols (or ketones) of the phenanthrene series (carrying the side chain in position 3) and of the dibenzofuran series (side chain in position 2) one finds:

$-COCH_2N(CH_3)_2$ 146 (phenanthrene) 192 (dibenzofuran)
192 more analgesic, more emetic, more convulsant

$-CHOHCH_2N(CH_3)_2$ 149 (phenanthrene) 193 (dibenzofuran)
193 more analgesic, somewhat more toxic and convulsant

$-CHOHCH_2N(C_2H_5)_2$ 150 (phenanthrene) 292 (dibenzofuran)
292 more analgesic, more convulsant, more toxic, but causes no excitement

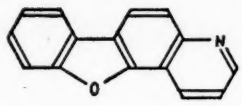
$-CHOHCH_2NC_5H_{10}$ 151 (phenanthrene) 194 (dibenzofuran)
194 not more analgesic, but more convulsant and definitely more toxic, causes no excitement

$-CHOHCH_2NH_2$ 286 (phenanthrene) 310 (dibenzofuran)
310 more analgesic and more emetic

The dibenzofurans of this series, like the corresponding phenanthrenes, usually quickened the respiratory rate, and often caused a brief initial rise in temperature, the only substance which did not do so being No. 310.

All the *amino ketones and amino alcohols* listed in table 18 were prepared by Mosettig and Robinson (*76*, *78*) by methods applied previously to analogous compounds in the phenanthrene series (see page 75).

(c) BENZOFUROQUINOLINES (PYRIDINODIBENZOFURANS)



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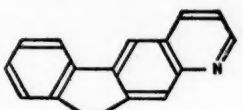

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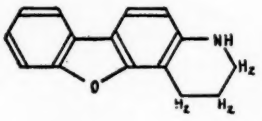

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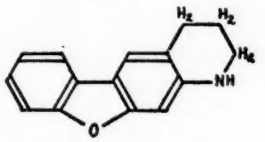

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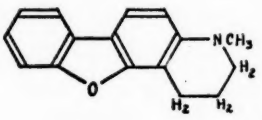

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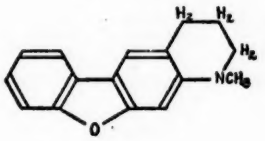

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TABLE 19.—*Benzofuroquinolines (pyridinodibenzofurans)*

	Percent base	M. p., °C.	Solubility in water	Analgesia	General depression	Incoordination	Emesis	Rectal temperature
230	85.7	240–265 (Base 105–106)	v. s.	N 200	S 200	N 300	None	300 (−) 1.5°
231	85.9	230–245 (Base 80–81)	m. s.[a]	N 300	S 200	N 300	200 (1) 165′	200 (−) 0.6°
232	86.7	196–215 (Base 72–73)	s.[b]	M 200	M 200	S 200	200 (2) 80′	200 (−) 0.7°
233	85.7	216–233 (Base 168–169)	v. s.[b]	S 300	S 200	N 300	200 (3) 92′	200 (−) 0.3°
234	85.9	196–226 (Base 111–112)	m. s.	N 300	S 200	N 300	200 (1) 15′	200 (+) 0.7°
235	86.7	198–205 (Base 56–57)	m. s.[c]	M 200	M 200	S 300	200 (3) 122′	300 (−) 0.6°

[a] Hydrolyzes on heating.
[b] Hydrolyzes strongly.
[c] Hydrolyzes.

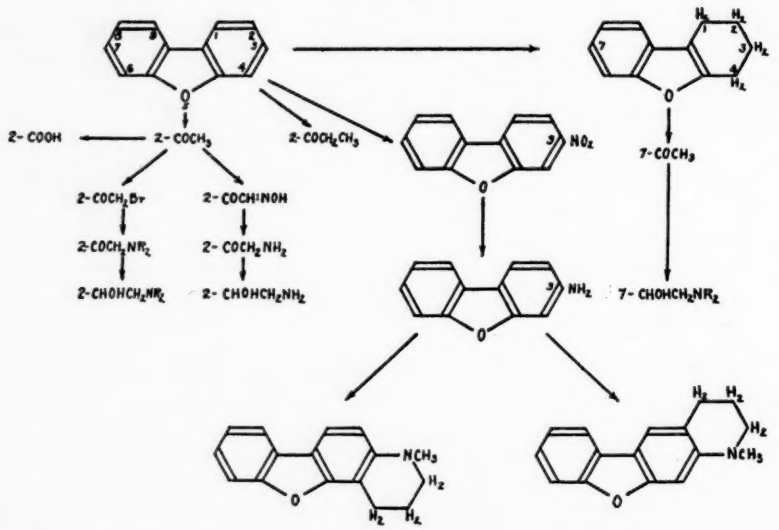
The group of benzofuroquinolines (table 19), as a whole, was less effective in every respect and less toxic than 3-aminodibenzofuran. The analgesic effect increased in both series from "quinoline" to "N-methyltetrahydroquinoline"; but in both series "tetrahydroquinoline" was least effective. There was very little difference between the two series (230–232 and 233–235).

The benzofuroquinolines and their derivatives were synthesized and elucidated in their structure by Mosettig and Robinson (*72*). Application of the Skraup method to 3-aminodibenzofuran yields the isomeric benzofuro[2, 3-f]-quinoline (230), and benzofuro[3, 2-g]-quinoline (233). High pressure reduction (chromite catalyst) leads to the corresponding tetrahydro compounds (231 and 234), the hydrogena-

tion attacking the pyridine nucleus only. Subsequent methylation gives the respective N-methyl-1, 2, 3, 4-tetrahydrobenzofuro[2, 3-f]-quinoline (232) and N-methyl-1, 2, 3, 4-tetrahydrobenzofuro[3, 2-g]-quinoline (235).

SUMMARY

Schematic review of the preparation of the principal compounds in the dibenzofuran series.



The most active compounds in the dibenzofuran series were again, as in the phenanthrene series, among the amino alcohols. Also, as in the phenanthrene series, the amino alcohols were more active than the corresponding amino ketones; the analgesic effect decreased from the tertiary, through the secondary to the primary amino alcohol; and of the tertiary amino alcohols the diethylamino was superior to the piperidino and dimethylamino compounds.

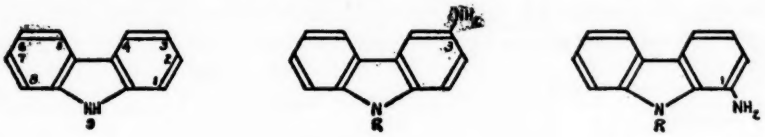
Quite uniformly the simple dibenzofuran derivatives, and especially the amino alcohols of the series, were more analgesic but at the same time more toxic and more convulsant than the corresponding phenanthrene derivatives, so that generally the margin of safety (ratio of analgesic to toxic dose) was about the same for both series. It must be pointed out that the correspondence holds only for the kind of substituent, not for its position, since the numbering of the dibenzofuran nucleus has no systematic or genetic relation to the numbering of the phenanthrene nucleus.

No conclusion can be drawn concerning the influence of hydrogenation on activity in the dibenzofuran series. There was no significant difference in activity between dibenzofuran and its tetrahydro derivative. Tetrahydroacetyldibenzofuran was decidedly more active

than the non-hydrogenated compound, but, on the other hand, the two corresponding diethylamino compounds of dibenzofuran and tetrahydrodibenzofuran were equally active. It should be noted, however, that the acetyl group and the alkamine side chain were in different positions in the hydrogenated and non-hydrogenated nucleus.

The attachment of a nitrogen-containing ring to dibenzofuran has, so far at least, not resulted in compounds with promising qualities.

(d) CARBAZOLE, AMINOCARBAZOLE, AND DERIVATIVES



$R = CH_3,\ C_2H_5,\ COCH_3$

TABLE 20.—*Carbazole, aminocarbazole, and its derivatives*

Position-substituent	Percent base	M. p., ° C.	Solubility grams in 100 cc water	Analgesia	Hours of duration	General depression	Incoordination	Emesis	Rectal temperature
408. Carbazole	100	247		N 300		S 100	S 200	N 300	300 (−) 0.5°
268 3-NH_2 [a]	83.3		[b] 1.5	S 40	5+	S 40	S 40	100 (2) 63′	30 (−) 1.2°
307 3-NH_2, 9-CH_3	84.3	285–293 vac., dec.	[c] 1.4	S 25	5+	[d] S 20	S 20	30 (1) 52′	20 (−) 1.4°
339 3-NH_2, 9-C_2H_5	85.2		[e] 0.5	S 25	5	S 15	S 15	20 (1) 41′	10 (−) 0.5°; 20 (−) 1.2°
374 3-NH_2, 9-$COCH_3$	86.0	245 vac., dec.	[f] 2.0	S 25	5	S 25	S 25	25 (2) 67′	20 (−) 0.8°; 30 (−) 1.2°
337 1-NH_2	83.3		[g] 1.0	S 40	5	S 30	S 30	N 75	30 (−) 0.5°; 40 (−) 1.2°
338 1-NH_2, 9-CH_3	84.3	Above 275	[g] 1.0	S 60	−5	S 50	S 50	60 (1) 42′	50 (−) 0.7°; 75 (−) 1.0°

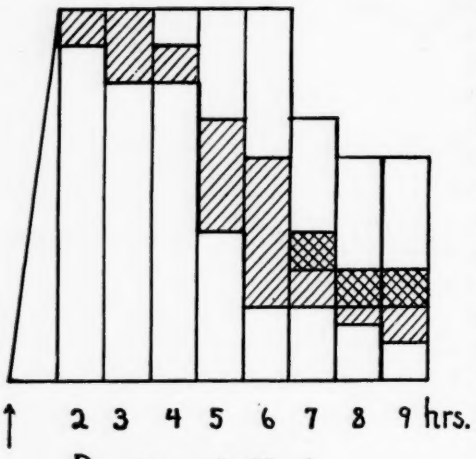
[a] The data for No. 268 to No. 338 refer to the hydrochlorides in which form the substances were administered.
[b] Some hydrolysis, slight turbidity; solution not very stable.
[c] Solutions not stable, turn blue in 24 hours.
[d] Pupils slightly dilated.
[e] Solutions not stable, sensitive toward light
[f] Slight hydrolysis.
[g] Slight hydrolysis only on warming.

The compounds grouped in table 20, except carbazole itself, showed a relatively high analgesic effectiveness when compared to simple amino phenanthrene derivatives. Very remarkable were the low toxicity, the duration of analgesic and depressant effects, the persistence throughout the group of the fall in temperature, and the relatively mild emetic action. There is also chemically a common characteristic throughout the series; the compounds are weak bases and their salts are hydrolyzed, more or less, in aqueous solution.

The two aminocarbazoles, Nos. 268 and 337, were practically identical in their effects. Methylation of the imino group (position

9) in the former increased its effect, while the same change in No. 337 decreased its activity. The effectiveness of No. 268 was increased in the same way by methylation, ethylation, or acetylation of the imino group. In fact, the action of the three substances, 307, 339, and 374, in the cat was qualitatively identical, and quantitatively nearly identical. Any one of these three substances affords an opportunity to illustrate the dissociation between analgesic and depressant actions because of differences in their time relationships. The incidence and duration of the principal effects of No. 307 have been plotted in the accompanying figure.

An exactly analogous figure could be made from the data of No. 339 or 374. The substance was administered orally in a dose of 25 mg per kg to each of ten cats and observations made at each hour thereafter. In the figure, the successive columns indicate hours after the administration of the drug, and the height of each column indicates the number of animals showing a particular effect at each hour. The incidence of analgesia among the group of ten animals is shown by the height of the lower unshaded portion of each column; the incidence of effect on rectal temperature, by the unshaded, plus the singly cross-shaded area; that of incoordination by the height of the column through the doubly cross-shaded area; and that of general depressant effect, by the total height of each column. For the group the average duration of quieting effect was 8.0 hours, of disturbance of coordination 6.0 hours, of fall in temperature 5.5 hours, and of analgesic effect 4.5 hours.



The incoordination with aminocarbazoles seemed to be a disturbance of equilibrium rather than muscular weakness such as is caused by hypnotics in general, since often the animals which had received one of this group were able to leap normally, when their gait was distinctly staggering and their ability to right themselves was subnormal. The aminocarbazoles quickened the respiratory rate regularly, often quickened the heart rate as well, and not infrequently caused the pupils to dilate slightly.

Carbazole.—Eastman's practical carbazole, 90–95 percent, was purified through the picrate, recrystallization from xylene, and sublimation in an oil-pump vacuum.

3-Aminocarbazole hydrochloride was prepared by reduction of the 9-nitroso-3-nitrocarbazole with stannous chloride and hydrochloric acid, according to the method of Ruff and Stein (*79*).

3-Amino-9-methylcarbazole hydrochloride (*82*).—The base, m. p. 174°, was prepared by the method of Lindemann (*80*) by methylation of 3-nitrocarbazole and subsequent reduction with stannous chloride in glacial acetic acid.

3-Amino-9-ethylcarbazole hydrochloride (*82*).—The base, m. p. 113–114°, was prepared analogously to the 9-methyl derivative (*80*) by ethylation of 3-nitrocarbazole and subsequent reduction.

1-Aminocarbazole hydrochloride was prepared by Small and Meitzner (*82*), using a novel and very practical method, through catalytic reduction of 1-nitro-3, 6-dibromocarbazole (*81*) with palladium-calcium carbonate catalyst, whereby simultaneously the bromine atoms are eliminated and the nitro group is reduced to the amino group. See also Lindemann and Werther (*83*), and Mottier (*84*).

1-Amino-9-methylcarbazole hydrochloride was prepared in an analogous way by catalytic reduction of 1-nitro-3, 6-dibromo-9-methylcarbazole (*81*, *82*). Melting point of base, 102.5°.

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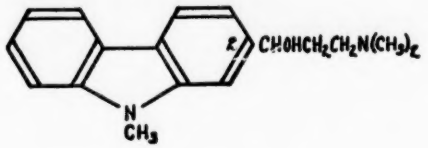
(e) AMINO- AND HYDROXY-TETRAHYDROCARBAZOLES AND AMINO ALCOHOLS DERIVED FROM CARBAZOLE



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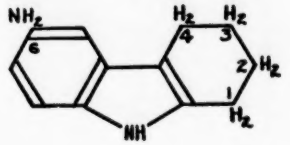

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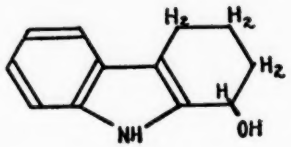

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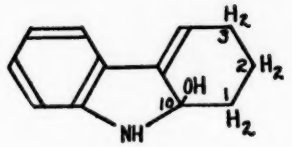

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TABLE 21.—*Amino- and hydroxy-tetrahydrocarbazoles, and amino alcohols derived from carbazole*

	Position-substituent	M. P., °C	Solubility	Analgesia	Hours of duration	General depression	Incoordination	Emesis	Rectal temperature
409	2-CHOHCH$_2$CH$_2$N(CH$_3$)$_2$[a] 9-CH$_3$	195–196 dec	30 g in 100 cc water	M 60 Inj. M 45	5+	[b] S 50 S 30	S 50 S 30	50 (3) 33′ [c] 30 (1) 25′	60 (−) 0.6°
421	2-CHOHCH$_2$CH$_2$(C$_2$H$_5$)$_2$[d] 9-CH$_3$	76.8	Insol. in water, sol. in dil. HCl	S 15 Inj. M 10	5+ 5+	[e] S 25	M 25	10 (3) 33′ 10 (3) 34′	25 (−) 0.5° 10 (−) 0.2°
317	6-NH$_2$[f] 1, 2, 3, 4-tetrahydro	152		M 60	5+	S 50	S 60	50 (1) 18′	50 (−) 1.2°
373	1-OH [f] 1, 2, 3, 4-tetrahydro	118.5	Insol. in water and dil. acids	S 100	5	S 80	S 50	50 (3) 52′	60 (−) 0.9°
372	10-OH [f] 1, 2, 3, 10-tetrahydro	153	Sol. in dil. HCl	N 300		S 100	S 100	200 (2) 40′	200 (−) 1.3°

[a] The data of this compound refer to the hydrochloride in which form the substance was administered; 88.6 percent base.
[b] Convulsion in 1 animal in 42′ after administration of 100 mg per kg.
[c] Of the 20 animals used, 50 to 100 mg per kg, 15 vomited.
[d] Administered by mouth as base, for injection dissolved in dilute HCl and neutralized.
[e] Convulsion in 3 animals with 50 mg per kg, 48′ after administration (average).
[f] Administered as base.

Of the two amino alcohols (table 21), the diethylamino was much the more active; it was in fact the most effective so far, in respect to analgesic action of our carbazole series. Both were quite emetic and both were convulsant; but their toxicity was not very great. In making comparisons it should be remembered that the alkamine side chain is in position -2.

6-Amino-1, 2, 3, 4-tetrahydrocarbazole was less analgesic than the corresponding nonhydrogenated compound, 3-aminocarbazole (268). No. 373 and particularly 372 were very low in activity; both have practically no basic character.

This group of carbazole derivatives, like those of group 20, caused a persistent fall in temperature.

2-[3-(Dimethylamino)-1-hydroxy-n-propyl] 9-methyl carbazole hydrochloride was synthesized by Small and Ruberg (*85*) by application of the Mannich reaction to 2-acetyl-9-methylcarbazole (*86*), (which had been prepared in a simplified manner), and subsequent catalytic reduction of the resulting amino ketone.

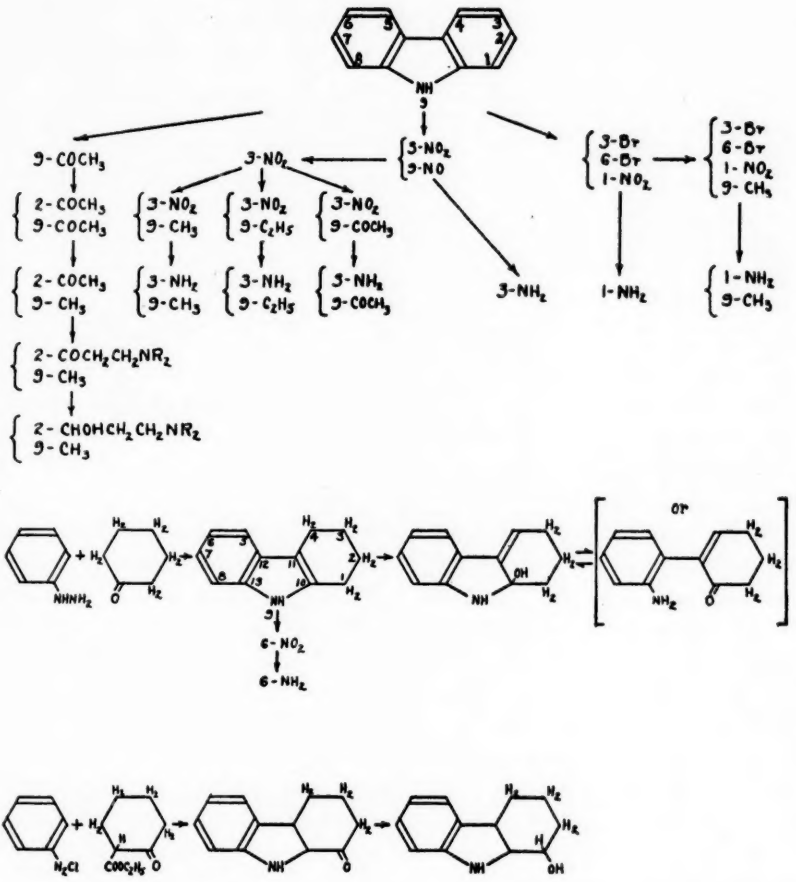
6-Amino-1, 2, 3, 4-tetrahydrocarbazole was prepared according to the directions of Perkin and Plant (*87*) by nitration of tetrahydrocarbazole and subsequent reduction of the nitro derivative to the amine.

1-Hydroxy-1, 2, 3, 4-tetrahydrocarbazole was obtained by catalytic reduction of 1-keto-1, 2, 3, 4-tetrahydrocarbazole (*82*). The keto-tetrahydrocarbazole was prepared according to Lions (*88*). See also Coffey (*89*), and Mears, Oakeshott, and Plant (*90*).

10-Hydroxy-1, 2, 3, 10-tetrahydrocarbazole was prepared according to Plant and Tomlinson (*91*) by bromination, removal of hydrogen bromide, and subsequent replacement of the remaining bromine by hydroxyl.

SUMMARY

Schematic review of the preparation of the principal compounds in the carbazole series.



All of this rather limited group of carbazole derivatives were general depressants, caused more or less incoordination, and brought about a moderate fall in temperature which persisted for more than 5 hours. All of them exhibited definite analgesic action; their toxicity was low, and they rarely produced vomiting. The aminocarbazoles were the most active members of the group; the activity of one of them (No. 268) was increased almost twofold by alkylation of the bridge nitrogen. One of the amino alcohols studied was less effective than the corresponding aminocarbazole; the other was the most actively analgesic of the carbazole series. The few tetrahydrocarbazole derivatives so far studied were relatively inactive.

CONCLUSIONS

1. The order of decreasing effectiveness, particularly in depressant and analgesic actions, of partially hydrogenated phenanthrenes is: 9, 10-dihydrophenanthrene, 1, 2, 3, 4-tetrahydrophenanthrene, 1, 2, 3, 4, 5, 6, 7, 8-octahydrophenanthrene, and phenanthrene. Octahydrophenanthrene and phenanthrene are practically identical in their action.

2. The activity of phenanthrene may be enhanced, even to the extent of exhibiting some analgesic action, by the addition of simple substituents. The most effective are hydroxy- and amino groups.

3. Simple derivatives carrying in position 3 -OH, $-NH_2$, $-COCH_3$, $-CH_2OH$, $-CHOHCH_3$, or -COOH, are in almost all respects more effective than the corresponding 2- or 9-derivatives.

4. Alkylation or acetylation of the mono- or poly-hydroxyphenanthrenes (including morphenol) decreases effectiveness decidedly. The same relation holds with the carboxylic acids and their derivatives, the esters and amides, and with methylation or acetylation of the amino group attached directly to the nucleus, whether the nucleus is phenanthrene, 9, 10-dihydrophenanthrene, or 1, 2, 3, 4-tetrahydrophenanthrene.

5. No generalization can be made as to the influence on pharmacological action of the entrance of another substituent in a given mono-substituted phenanthrene. There is a decided increase in effectiveness from 3-hydroxyphenanthrene to 3, 4-dihydroxyphenanthrene and from 3-hydroxy- to 3-hydroxy-4-amino-phenanthrene, but 3-hydroxy-9-amino- and 9-hydroxy-10-amino-phenanthrene are less effective than compounds containing either substituent alone.

6. An interesting side action is seen to a greater or less degree with many phenanthrene derivatives carrying a substituent in position 9. This consists in a particular type of incoordination, characterized by veratrine-like delayed relaxation. It is particularly apparent with the 9-carboxylic acid and its derivatives.

7. Among the amino alcohols carrying the nitrogen and the alcoholic hydroxyl in a side chain the diethylamino alcohols show, generally, the highest analgesic and depressant action, the dimethylamino derivatives are least active, and the piperidino compounds are usually intermediate; the last are often the most toxic. Comparatively the py-tetrahydroisoquinolino derivatives are exceedingly low in analgesic action.

8. The amino alcohols of type $-CHOHCH(CH_3)NR_2$ are, generally, less active than the lower homologs, $-CHOHCH_2NR_2$, and the latter are less active than the propanolamines of the type, $-CHOHCH_2CH_2NR_2$.

9. The primary amino alcohols are much less effective than the tertiary alcohols, but are more emetic.

10. No definite conclusion can be drawn as to the effect of introducing a phenolic group into the phenanthrene nucleus of these amino alcohols.

11. The amino alcohols derived from 9, 10-dihydrophenanthrene are, with the exception of the tetrahydroisoquinolino derivatives, highly analgesic, but are very convulsant.

12. The amino alcohols derived from symmetrical octahydrophenanthrene are locally irritant, since vomiting occurred very soon after oral administration. This interferes with correct evaluation of their activity.

13. The most powerful synthetic analgesics are among the cyclic amino alcohols derived from tetrahydrophenanthrene. Here the isoquinolino derivatives show an activity equal to or higher than that of the other members of their respective groups. One of them (No. 407) produces in the cat a very typical morphine-like picture without evidence of convulsant action and almost without any emetic effect.

14. The most active compounds in the dibenzofuran series are among the amino alcohols. These are more active than the corresponding amino ketones; the analgesic effect decreases from the tertiary through the secondary to the primary amino alcohol; and of the tertiary amino alcohols the diethylamino is superior to the piperidino and dimethylamino compounds. These results parallel the findings in the phenanthrene series.

15. The simple dibenzofuran derivatives, and especially the amino alcohols of the series, are more analgesic but also more toxic and more convulsant than the corresponding members of the phenanthrene series, making the margin of safety (ratio of analgesic to toxic dose) about the same in both. The correspondence holds only for the kind of substituent, not for its position, since the numbering of the dibenzofuran nucleus has no systematic or genetic relation to the numbering of the phenanthrene nucleus.

16. The attachment of a nitrogen-containing ring to dibenzofuran has, so far at least, not resulted in compounds with promising qualities.

17. All of the limited group of simple carbazole derivatives studied are general depressants, cause more or less incoordination, and bring about a moderate fall in temperature which persists for more than 5 hours. All of them exhibit definite analgesic action, their toxicity is low, and they rarely produce vomiting.

18. The aminocarbazoles are very active members of the group; the activity of one of them is increased almost twofold by substituting the hydrogen of the imino group with ethyl or acetyl.

19. One amino alcohol studied is less effective than the corresponding aminocarbazole; the other exhibits definitely greater analgesic power. Both are, however, convulsant and quite emetic.

20. The tetrahydrocarbazole derivatives are relatively inactive.

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PART III. CLINICAL STUDIES OF DRUG ADDICTION, WITH SPECIAL REFERENCE TO OPIUM DERIVATIVES AND ALLIED SYNTHETIC SUBSTANCES

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1. Introduction

The purpose of the studies of drug addiction being carried on by the United States Public Health Service is to develop better methods for its prevention and treatment. With these ends in view two main avenues of approach have been undertaken: (1) Research into the true nature of drug addiction, and (2) a cooperative search for a non-addicting substance which possesses the clinically desirable attributes of morphine. The latter approach involves a study of the relationship of the structure of morphine, and chemically related opium compounds, and allied synthetic substances to the development of addiction.

The hypothesis of a relationship between chemical structure and the various effects of morphine, including the production of addiction, has been discussed in another section (*1*), but the studies summarized in connection with that discussion have dealt only with the effects of single doses of the various substances investigated. However, in the administration of these drugs to man, the effect of single doses is not the important consideration from the standpoint of addiction. In man and animal, tolerance and addiction are developed by repeated and often very prolonged administration, though the time required will vary with the nature of the addictive substance and other factors. Different species vary widely in their natural tolerance to morphine and in the ease with which they acquire additional tolerance; and they vary even more widely in the ease with which they become physically dependent to morphine, and in this respect man apparently stands

first. Obviously, then, the extension of the study of suitable substitutes for morphine to their administration, and especially their repeated administration to man, is essential, and methods to this end have been devised. To carry out such studies the United States Public Health Service offered both a wealth of clinical material and unique opportunities for carefully controlled studies at the United States Penitentiary Annex, Fort Leavenworth, Kansas, and at the United States Public Health Service Hospital, Lexington, Ky.

Certain compounds related to morphine and certain allied synthetic substances have been studied in an attempt to detect the presence or absence of the addiction factor in them, and to learn, if possible, whether this factor is related to a particular chemical structure. In other words, it is hoped that through these studies it will be possible to demonstrate a dissociation of the addiction factor from the other properties of morphine, and to identify this factor with some part of the chemical structure, in either the nucleus or outlying groups.

2. Definitions

The following definitions are presented at this point for the purpose of insuring uniform interpretation of the material to be reported and discussed:

Addiction to opiates embraces three intimately related, but distinct, phenomena: namely, *tolerance*, *habituation*, and *dependence*. It should be emphasized that this is an artificial separation made for the purposes of description, and that the phenomena which make up the psycho-somatic complex known as addiction are intricately interwoven and interdependent.

By *tolerance* is meant the gradual decrease in the effect produced by repeated administrations of a drug; or, conversely, a gradual increase in the dosage of the drug necessary to produce the same effect as did the initial dose (*2*). It is probably true that tolerance ultimately becomes of such magnitude that the effect of the initial dose cannot be reproduced by excessive doses.

By *habituation* is meant the psychical phenomenon of adaptation and mental conditioning to the repetition of an effect. Habituation to opiates is probably more intense than habituation to other substances. In a sense, habituation represents psychical dependence.

Dependence is the term used to denote the distortion of normal physiologic processes which result from prolonged administration of addicting drugs, and which is manifested by the necessity for the presence of an adequate amount of one of these drugs in the body for the maintenance of physical equilibrium. The presence of dependence can be established only by the appearance of the characteristic syndrome of abstinence phenomena subsequent to withdrawal of drugs capable of maintaining dependence. Dependence as distin-

guished from habituation is physical rather than psychical. Since dependence to drugs other than the derivatives of opium in which the phenanthrene nucleus is present has not been satisfactorily demonstrated, it is safe to consider dependence as peculiar to this group of narcotics.

Experience would lead one to believe that dependence rarely becomes so intense that opiates are necessary to the maintenance of life; that dependence develops gradually in the human being, reaching a high degree of intensity, in the uninitiated, in approximately 6 months; that it gains in intensity slowly after reaching this level; and that its development is favored more by regularity of administration than by the amount of the drug or the route of its administration. The rhythm most suitable to the development and maintenance of dependence is based on the duration of dependence producing action of the particular opiate employed. Although dependence is intimately associated with tolerance and habituation, the intensity of these latter phenomena may be disproportionate to that of the former.

3. Addiction Liability Studies

(a) METHODS

There are two methods by which the presence of the addiction factor in the substances to be investigated may be demonstrated:

1. Attempt to produce physical dependence in non-addicted individuals through regular and prolonged administration of the compounds in question. This method would be best, but has obvious disadvantages.

2. Observe, when the compounds in question are substituted for morphine, whether they maintain preestablished physical dependence upon morphine.

Experience indicates that no substances other than compounds chemically related to morphine will satisfy and maintain physical dependence to morphine. It is true that certain phenomena of abstinence which follow withdrawal of morphine can be suppressed, aborted, or masked by other pharmacological agents; but these substances do not produce the clinical picture of normality which follows the administration of an adequate dose of morphine to an addict. Hence, it seems reasonable to suppose that satisfaction and maintenance of dependence may indicate the presence of the addiction factor; that is, a substance which will satisfy and support physical dependence should be considered to be capable of producing it.

The method of substitution, based on this hypothesis, has been used in these clinical investigations. In practice the following technique has been adhered to in the prosecution of the substitution

studies: Following their admission to the hospital, addicts are observed closely and frequently for objective signs of abstinence and are given no narcotic until evidence of valid dependence has been demonstrated. Then stabilization of the addict on morphine is accomplished by administering amounts adjusted so that the addict shows evidence of neither abstinence nor overdosage. Stability, or morphine balance, is achieved by reducing the amount of morphine until abstinence phenomena appear, and then increasing it until they disappear, thus giving the minimum amount required for maintenance of comfort.

Stability, of course, is hardly an adequate term to use in this connection, for the state of physical dependence is a more or less artificial condition in which a constant ebb and flow is taking place between the approximate normality of the dependence satisfied state and the abnormality of the abstinence syndrome. In other words, physical dependence might be considered as a condition of constantly impending abstinence which can be prevented or relieved temporarily by adequate doses of morphine or one of its addictive derivatives. Thus it is difficult to conceive of physical dependence so stabilized as to compare with the plateau of true normality. This concept is illustrated in figure 1. The aim of stabilization is to approximate normality as nearly as possible through the proper spacing and amounts of the doses administered. It should be pointed out that meeting the physical requirement in this manner does not necessarily satisfy the emotional requirement; that is, habituation is sometimes more intense than physical dependence. In other words, the psychical component of the psycho-somatic complex of addiction may be of greater intensity in some individuals than the physical component.

After a period of stabilization on morphine for not less than 7 days, the substance in question is completely substituted for morphine in doses which are considered safe and adequate on the basis of the pharmacological studies. The doses and the intervals of their administration are then adjusted so that dependence is maintained as nearly as possible at the same level of stability as when the addict was receiving morphine. A substitution period of 7 days or more is considered to be ample, and after 1 to 2 weeks of complete substitution, administration of the substituted compound is discontinued. Observations for manifestations of abstinence are continued for 1 to 2 weeks following withdrawal. Thus the substance in question can be compared with morphine in respect to dosage, approximate duration of dependence satisfaction, adequacy of addiction satisfaction, and the character and duration of the abstinence syndrome. Although the methods of observation and evaluation of the abstinence syndrome have been improved considerably since these studies were started in 1933, no changes in the technique of carrying out the substitution program have been found necessary.

It has been stated that the diagnosis of physical dependence is made on the basis of the abstinence phenomena which appear following withdrawal of narcotics from addicted individuals. These phenomena may also be used to estimate the intensity of physical dependence. Some of the signs characteristic of the abstinence syndrome

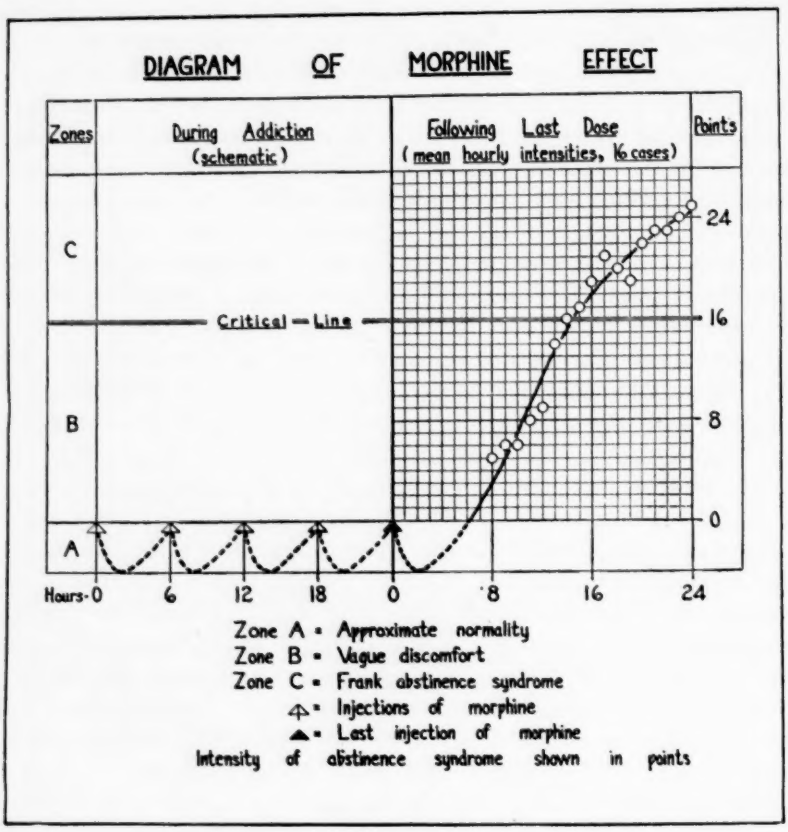

FIGURE 1.

are shown in table 1, listed in the approximate order of their appearance following withdrawal and grouped according to their significance in estimating the intensity of the abstinence syndrome.

TABLE 1.—*The abstinence syndrome*

Mild, or +	*Marked*, or +++
Yawning.	Fever.
Lacrimation.	Increase in respiratory rate.
Rhinorrhea.	Restlessness.
Perspiration.	Insomnia.
Moderate, or ++	*Severe*, or ++++
Muscle tremor.	Vomiting.
Gooseflesh.	Diarrhea.
Loss of appetite.	Weight loss.
Dilated pupils.	

There are many other signs and symptoms of drug deprivation which are not listed in this table, and which have not been used in abstinence syndrome evaluation. Methods for observation and evaluation have been described in considerable detail elsewhere (*3*, *4*). The intensity of the abstinence syndrome may be estimated in degree from *Mild* (+) to *Severe* (++++) by use of table 1, or it may be scored in points by assigning numerical values to certain of the manifestations. It is obvious, of course, that the groupings used in the degree method are not sharply defined, but shade one into another as the intensity of the syndrome waxes and wanes.

The point system of abstinence evaluation shown in table 2, and which has been described in another paper (*4*), takes into account those signs which are most accurately measurable, and requires a short period of stabilization for the purpose of acquiring base-line data (addiction means) on rectal temperature, respiratory rate, caloric intake, and blood pressure. Temperatures and respiratory rates are determined three times daily; weight and blood pressure are measured every morning before breakfast; and caloric intake is obtained by weighing the food eaten and estimating its caloric value by the use of standard tables. Abstinence fever, rise in respiratory rate, loss of appetite, and rise in blood pressure are scored by allowing certain numerical values for the extent of their daily deviations from addiction means. Weight loss is measured from the last day of addiction. Except for emesis, the signs listed can receive only one score each per day. Diarrhea and insomnia were not included in this system because of the difficulties involved in measuring them accurately, and to keep the system simple.

TABLE 2.—*Daily evaluation of abstinence syndrome intensity by the point system*

Signs	Points	Signs	Points
Yawning	1	Temperature (daily average) each 0.1° C. increase over addiction mean	1
Lacrimation	1	Respiration (daily average) each respiration per minute over addiction mean	1
Rhinorrhea	1	Systolic B. P. (a. m.) each 2 mm Hg rise over addiction mean (15 point limit)	1
Diaphoresis	1	Weight (a. m.) each pound lost from last addiction day	1
Anorexia (40% drop)	3		
Mydriasis	3		
Tremor	3		
Gooseflesh	3		
Restlessness	5		
Emesis (each)	5		

Total abstinence syndrome intensity per day is sum of points scored.

This method has the advantage of being thoroughly impersonal and completely objective, but it has the obvious disadvantage that the points assigned to the various phenomena are purely arbitrary. It is, however, based upon experience with a very large number of addicts, and has been shown to agree quite closely with the degree method (*4*). By deleting the scores for weight loss and anorexia, and limiting the

scores made on blood pressure, temperature, and respiration to 10 points each, this system is used to detect changes in intensity of the abstinence syndrome which occur during periods of 1 hour or less. This modification of the point system for periods of less than 24 hours was used in obtaining the data on the onset of the abstinence syndrome shown in figure 1.

(b) RESULTS

To facilitate description, and for the sake of brevity the results have been summarized and are presented in the form of a table (table 3), listing the findings on morphine and chemically related compounds which are considered to be most important from the standpoint of addiction. This arrangement permits ready comparison of the substituted derivatives with morphine and with one another in the following respects:

TABLE 3.—*Comparison of results with morphine and chemically related compounds*

Group	No. of drug	Name of drug	No. of cases	No. of days of complete substitution	Dosage of substituted drug: No. of injections per day	Dosage of substituted drug: Duration of dependence satisfaction (hours)	Dosage of substituted drug: Daily amount in relation to morphine	Adequacy of addiction satisfaction by substituted drug	Abstinence syndrome following withdrawal of substituted drug: Onset	Abstinence syndrome following withdrawal of substituted drug: Intensity in relation to morphine	Abstinence syndrome following withdrawal of substituted drug: Duration
									Hours		*Days*
I	2	Codeine	7	8–14	4	6 or more	±5	Adequate*	±20	As severe	±8
	3	Pseudocodeine	6	7–14	4	do	±10	do*	±18	Less severe	±7
	36	Isocodeine	2	7	4	do	±6	do*	±18	As severe	±7
II	265	Dihydro-α-isomorphine	5	7	4	do	±0.5	Complete	±18	Less severe	±
	128	Diacetyldihydromorphine	5	7–27	4	do	±0.5	do	±18	As severe	±8
	371	Dihydrocodeinone enol acetate (Acedicon)	5	8	4	do	±1	do	±18	do	±8
	87	Dihydrocodeine methyl ether	4	7–9	4	do	±1	do	±18	Less severe	±8
	236	α-isomorphine	4	7	4	do	±1	do	±16	do	±7
	143	Morphine	±100		4	±6			±14		±8
	322	Dihydrohydroxycodeinone (Eukodal)	3	7	4	±6	±1.5	Complete	±14	As severe	±8
	51	Dihydroisocodeine	4	8–11	5	±5	±5	do	±12	do	±8
III	123	Dihydromorphinone (Dilaudid)	7	12–17	*4	±3	*±0.25	Complete	±10	As severe	±5
	126	Dihydrodesoxymorphine-D	5	8–21	*4	±3	*±0.5	do	±8	do	±5
	112	Dihydroheterocodeine	7	7–11	6	±3½	±0.4	do	±9	do*	5–7
	398	Methyldihydromorphinone	7	7–10	8 or 9	±2	±0.2	do	±3	do	5–7
	142	β-chloromorphide	5	7	5–7	±2	±3	Adequate*	±5	do	5–7

*See text.

±=Approximately.

1. *Dosage.*—The number of injections required per day to maintain stability (a factor which is considered to be as important as the amount needed) is based to a large extent on the duration of action of the particular substance administered in preventing the appearance of abstinence signs. With morphine, this effect lasts not much more than 6 hours; hence, four doses per day are required. It will be noticed that the number of injections required per day by the majority of the compounds studied was four, and that in most of these the duration of dependence satisfaction is given as 6 hours or more. It is possible that some of these are effective for 7 or 8 hours, but this was not determined. The effect of dihydrohydroxycodeinone (Eukodal) lasted not much more than 6 hours, and that of dihydroisocodeine about 5 hours. In the cases of dihydrodesoxymorphine-D and dihydromorphinone (Dilaudid), compounds that satisfied dependence for not much more than 3 hours, it was attempted to produce stability by increasing the amounts administered. With the other compounds of brief action, however, the number of injections per day was increased in order to maintain stability. This was fairly effective in the case of dihydroheterocodeine, but not so satisfactory with β-chloromorphide and methyldihydromorphinone.

The actual amounts of the substitutes administered are not shown, but rather the group mean amount of the substitute required per day for the maintenance of stability in relation to the mean amount of morphine required by that group prior to the substitution. In making this comparison morphine was given the value of 1. Thus, from the standpoint of dependence satisfaction, it will be noticed that codeine, for example, is about one-fifth as potent as morphine, whereas, dihydro-α-isomorphine is about twice as potent as morphine. The relative amounts given for dihydrodesoxymorphine-D and dihydromorphinone (Dilaudid) are not accurate because of the attempts to prolong their actions by increasing the amounts administered.

(2).—*Adequacy of addiction satisfaction by the substituted compounds.*—The term addiction is used here in its broad sense which includes *tolerance*, *habituation*, and *dependence*.

Tolerance.—Two of the drugs showed effects early in the substitution period to which morphine had not given complete cross-tolerance. All of the patients who received β-chloromorphide complained of burning at the sites of injections. No remarkable tolerance to this effect developed. Two of the cases had severe reactions to injections of β-chloromorphide, consisting of scintillating scotomata, generalized hot flashes, profuse perspiration, and nausea and vomiting. This reaction started 7 minutes after the subcutaneous injection and lasted about 30 minutes. However, with each injection the reactions became less severe, and the development of complete tolerance to these effects took 3 days in one case and 5 days in the other. In several of the

patients, the first few injections of codeine were followed by local and general flushing and itching of the skin which lasted about an hour.

Habituation.—Prevention and relief of the psychical manifestations of abstinence were obtained through the administration of all of the morphine-like substances employed except those listed in group I of table 3. Codeine, pseudocodeine, and isocodeine were considered to be inadequate in this respect; for with these drugs the patients stated, in effect, that the injections relieved their pain and aches and made them sleepy, but there was "something missing," and they did not appear to be as emotionally content as when they were receiving morphine. Although the increased number of injections and brief duration of satisfaction which attended substitution of β-chloromorphide and methyldihydromorphinone, and the reaction to β-chloromorphide were emotionally disconcerting to some of the patients, habituation satisfaction by both substitutes was adequate.

Dependence.—Signs of abstinence were prevented by or disappeared after injections of all of the morphine-like compounds which were administered. The duration of dependence satisfaction by these compounds is considered under (1) *Dosage.*

(3) *The abstinence syndrome which followed withdrawal of the substituted drugs.*—Three features of the abstinence syndrome seem to offer the best means for comparison; namely, *onset, intensity,* and *duration.*

Onset.—The number of hours which have elapsed between administration of the last dose of the substitute and the appearance of definite signs of drug deprivation—that is, abstinence syndrome intensity of 15 to 17 points—is called onset. With morphine, this occurs about 14 hours following the last dose. By that it is not meant that the abstinence syndrome appears suddenly at this time; for, during the period which elapses between the expiration of dependence satisfaction and the onset of definite signs of abstinence, both the patient and observer are conscious of progressive discomfort which gradually becomes more tangible, and finally is clearly objective and measurable in its intensity. This is illustrated in figure 1.

With nine of the morphine-like compounds investigated, the onset was equal to or slower than with morphine; with five it was definitely shorter (group III, table 3) and with one it was intermediate. There seems to be a direct relation between the time of onset of abstinence and the duration of dependence satisfaction.

Intensity.—The abstinence syndromes which appeared following withdrawal of pseudocodeine, α-isomorphine, dihydro-α-isomorphine, and dihydrocodeine methyl ether appeared to be less severe than the syndrome of morphine abstinence. By this it is not implied that these syndromes were of a mild character, but that their intensities were slightly, but definitely, less severe than the syndrome caused by

morphine abstinence. The abstinence syndrome which followed withdrawal of dihydroheterocodeine seemed slightly more intense than that of morphine.

Duration.—The group mean number of days which elapsed between withdrawal and the disappearance of signs of abstinence is given as duration. It is not meant that in 5 to 8 days the patients were well, because it actually takes several months of abstinence for a patient to regain normality, but that in 5 to 8 days the abstinence syndrome was practically spent and evidences of recovery were obvious.

Following withdrawal of morphine, most of the signs of drug deprivation have disappeared by the eighth day. It will be noticed

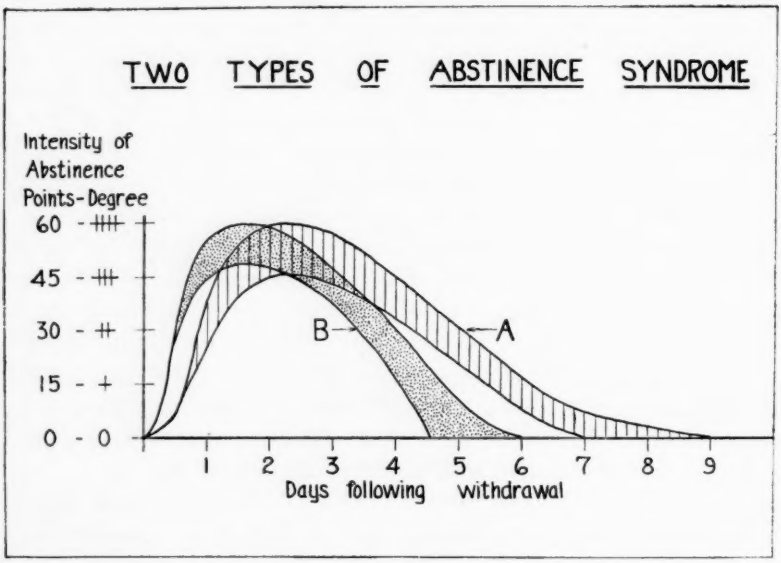

FIGURE 2.

that the majority of the substances listed in table 3 were about equal to, and none exceeded, morphine in this respect. Recovery after use of the shorter acting compounds (group III) was usually somewhat quicker than from the longer acting compounds (groups I and II).

A diagrammatic representation of the two types of abstinence syndromes seen following withdrawal of the compounds (listed in table 3) is shown in figure 2. The spread of the curves gives a rough indication of the ranges encountered. The curve labeled type "A" represents the abstinence syndromes which are practically indistinguishable from that following withdrawal of morphine, and shows what happens following withdrawal of the compounds listed in groups I and II. The curve indicated as type "B" represents the syndromes which follow withdrawal of the compounds listed in group III. It will be noticed that the syndrome typical of the compounds

in group III shows a quicker onset and somewhat shorter duration than the syndrome characteristic of the compounds in groups I and II.

In addition to the morphine-like compounds listed in table 3, two allied synthetic substances, 3-(1, 2, 3, 4-tetrahydroisoquinolino-)-4-hydroxy- 1, 2, 3, 4-tetrahydrophenanthrene (No. 259) and 6, 7-diethoxy-1-(3′, 4′-diethoxybenzyl)-isoquinoline ("Perparin") have been studied in regard to addiction liability. Neither of these substances exhibited any ameliorative effect on the abstinence syndromes which occurred when they were completely substituted for morphine in presumably effective amounts, nor did any recrudescence of the abstinence syndromes occur following their withdrawal. The findings in regard to "Perparin" were made the subject of another report (*5*).

(c) DISCUSSION

On the basis of these data and experience, the 15 morphine-like compounds, studied in the manner described and the amounts administered, were divided into three groups (table 3) according to whether they appeared to be more or less apt to produce addiction than morphine, or about equal to it in this respect.

Group I.—Codeine, pseudocodeine, and isocodeine were considered to be separable from the compounds comprising groups II and III because they did not seem to satisfy habituation, though it is true that this distinction is based to a large extent on subjective information. Experience indicates that codeine is an addictive drug (*6*), but it is well known that its addiction liability is less than that of morphine. Codeine addiction occurs infrequently probably because it produces relatively little euphoria, and thus is less desirable to the potential addict, and because codeine is relatively expensive and bulky in effective amounts. In these investigations pseudocodeine and isocodeine seemed more akin to codeine than morphine, hence, they were classified with codeine as drugs considered to be less addictive than morphine. It is not possible to estimate how much less addictive they are because these studies have been largely qualitative. Chemically these drugs are members of the *codeine* series possessing phenolic hydroxyls which have been muzzled by methylation, and unmodified alcoholic hydroxyls. They differ from each other only in the position of the alcoholic hydroxyl on the molecule.

Group II is composed of those substances which resembled morphine so closely in addiction effects that they were not readily distinguishable from it. Dihydroisocodeine appeared to be more or less intermediate, but was placed in group II because it resembled this group more closely than group III. It is possible that more comprehensive substitution studies of a semiquantitative nature might separate the compounds into more closely defined classes.

Chemically, four of the drugs in group II are members of the *codeine* series but they differ from those of group I in that all have been hydrogenated, and three have modified alcoholic hydroxyls. The other drugs in this group are members of the *morphine* series. The chemical modifications of group II which distinguish it from group I are those which have been shown (*1*) to increase pharmacologic activity.

Group III is composed of the substances characterized by brief pharmacological action. Chemically all of this group are members of the *morphine* series with modified alcoholic hydroxyls, and all except β-chloromorphide have been hydrogenated. In methyldihydromorphinone a methyl group has been attached to the nucleus, probably at carbon-7. The compounds of this group, other than β-chloromorphide, are also more powerful and rapidly acting than morphine. This increase in pharmacological activity appears to extend into the realm of addiction, for in a general way it seems that the tendency of morphine derivatives to produce dependence increases with the chemical alterations which cause increased potency and speed of action along with *shortened analgesic action.* Such changes result in much smaller clinical doses, but necessitate more frequent administration for the control of pain. The development of dependence appears to be favored by stepping up the injection rhythm, for dihydrodesoxymorphine-D (*7*), dihydromorphinone (Dilaudid) (*8, 9*), and dihydroheterocodeine [1] produce dependence more rapidly than morphine when administered regularly for the continuous relief of chronic pain.

Methyldihydromorphinone and β-chloromorphide differ from these three drugs in certain chemical and pharmacological features which appear to offer some hope that a dissociation of the dependence producing factor from the other properties of morphine may be accomplished at little or no expense of analgesic action. Chemically they have outlying groups attached to the molecule in new positions, and animal experiments on the duration of analgesic action indicate that they equal morphine in this respect (*1*). Should this latter feature carry over to man, we would have for the first time compounds with analgesic action that exceeds dependence satisfying action. It would seem that the development of dependence would be less likely to result from the clinical use of such compounds than from one like morphine, in which the dependence satisfying action outlasts its analgesic effect. The ideal morphine substitute would appear to be one in which analgesia lasting 5 hours or more is retained, but the dependence satisfying action is reduced to 30 minutes or less, or better still, is completely absent.

[1] In one patient, who had a carcinoma of the prostate with painful bone metastases, dihydroheterocodeine was administered regularly for the control of pain. Evidence of physical dependence was present on the fifteenth day of administration.

Because of the hope offered by methyldihydromorphinone and β-chloromorphide the clinical studies have been extended so that now they include accurate determinations of the duration of analgesic and dependence satisfying actions in addition to the usual substitution. Through the relationships found between analgesia and dependence it is hoped that more definite degrees of addiction liability may be postulated for the compounds studied in the future. This in turn would permit of more specific inferences as to the influence of chemical structure on addiction than are possible at present, and might serve as a guide to future chemical researches.

The extension of these studies includes electroencephalographic determinations of the comparative cortical effects of these compounds during the stabilization and substitution periods, and following withdrawal. These studies strongly suggest that changes in chemical structure affect the cerebral cortex in quantitatively and qualitatively different manners, and that cortical activity is altered during the withdrawal period.

It seems highly improbable that either 3-(1, 2, 3, 4-tetrahydroisoquinolino-)-4-hydroxy-1, 2, 3, 4-tetrahydrophenanthrene (No. 259) or 6, 7-diethoxy-1-(3′, 4′-diethoxybenzyl)-isoquinoline ("Perparin") possesses any addiction liability whatever, since neither substance had any effect on the abstinence syndrome while being administered or following its withdrawal.

4. Pharmacologic Clinical Studies

Studies of the analgesic action of methyldihydromorphinone are being carried out by F. E. Boys, J. W. Logie, and A. Becker, at the University Hospital, Ann Arbor, Mich., under the supervision of Nathan B. Eddy. Their unreported findings, based on the administration of over 400 doses of methyldihydromorphinone to more than 100 patients, indicate that this compound gives complete relief of pain within 10 to 20 minutes after subcutaneous injections of 7 mg, and that the analgesia lasts more than 2 hours. A sedative effect and partial relief of pain continued for a longer time. Relief of pain sometimes followed injections of as little as 1 to 2 mg. With none of the doses used has there been any evidence of a depressant effect on respiration, of an emetic action, or of any other untoward result. In one case, a patient with an inoperable lymphoblastoma which was causing severe pain and cough, who had been receiving previously two doses of Pantopon per day, methyldihydromorphinone was administered repeatedly during a period of 1 month. At the outset the dose employed was 2 mg, but because relief was incomplete, alternate doses of Pantopon (22 mg) or morphine (16 mg) were given. After the dose of methyldihydromorphinone had been raised to 4 mg, the patient was kept comfortable for 2 weeks by two injections daily of this drug

alone. Although no signs of tolerance or dependence were detected in this case, not enough of the drug was administered to justify any conclusion as to its addiction liability. The clinical results on the analgesic effectiveness of methyldihydromorphinone do not seem to agree with the analgesic effect in animals previously reported (*1*) in respect to either intensity or duration of action. However, the criteria of effect in the two studies are very different and this difference may account for the apparent discrepancy. In animals the effective analgesic dose is based upon the smallest recognizable depression of pain sense, and in the determination of duration of effect this same criterion is used. In the clinical studies, on the other hand, a very rigid standard of complete relief of clinical pain is employed since we have no other means of evaluating in acutely ill patients a lesser degree of analgesic action. Also the duration of clinical analgesic effect is the duration of complete relief.

Carefully controlled clinical observations on cough relief by codeine and dihydroisocodeine are being carried out by Lowrey F. Davenport, at the Middlesex County Tuberculosis Sanitorium, Waltham, Mass. His unreported results indicate that codeine and dihydroisocodeine are about equally effective against cough, and that, except in patients with very productive coughs, the uniformly effective oral dose of either drug is 10 mg. The antitussive action could be prolonged slightly by increasing the doses to 30 mg. These observations are noteworthy because they establish the minimal antitussive dose of codeine at 10 mg whereas 15 to 30 mg is the usual clinical dose range. The longest period of repeated administration of dihydroisocodeine in any case was 2 months, which is not long enough to permit conclusions as to the development of tolerance and dependence.

5. Conclusions

From observations made on addicts, involving the substitution of 15 related compounds for morphine, it is concluded that:

1. All of the compounds studied possess addiction liability.
2. Changes in the chemical structure of morphine alter the degree of addiction liability and other pharmacological actions in the same direction, but possibly not to the same extent.

From observations made on addicts, involving the substitution of 3-(1, 2, 3, 4-tetrahydroisoquinolino-)-4-hydroxy-1, 2, 3, 4-tetrahydrophenanthrene and 6, 7-diethoxy-1-(3′, 4′-diethoxybenzyl)-isoquinoline ("Perparin") for morphine it is concluded that neither of these synthetic substances possesses addiction liability.

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INDEX

Page

Abstinence syndrome 118, 122
Acedicon. *See* dihydrocodeinone enol acetate.
Acetocodeine types 29
Acetylallopseudocodeine 10, 19, 28
Acetylation—Morphine series 10, 19
Acetylation—Phenanthrene series 49, 74, 79, 80, 81, 88
Acetylcodeine 10, 19, 27
Acetylcodeine isomers. *See* under Isomers.
Acetyldemethylodihydrothebaine (same as Acedicon) 69
Acetyldihydroallopseudocodeine 19, 28
Acetyldihydrocodeine 10, 19, 27, 28, 31
Acetyldihydroisocodeine 19, 27, 31
Acetyldihydromorphine. *See* Monoacetyldihydromorphine.
Acetyldihydropseudocodeine 19, 28
Acetylhydroxycodeinone 31
Acetylisocodeine 10, 19, 27
Acetyl-α-isomorphine. *See* Monoacetyl-α-isomorphine.
Acetyl-β-isomorphine. *See* Monoacetyl-β-isomorphine.
Acetyl-γ-isomorphine. *See* Monoacetyl-γ-isomorphine.
Acetylmorphenol 48, 51
Acetylmorphine. *See* Monoacetylmorphine.
Acetylmorphine isomers. *See* under Isomers.
Acetylphenanthrenes 61, 62
Acetylpseudocodeine 10, 19, 28
Acetylthebaol 48, 50
Acylnaphthalenes 64
Addiction—Definition 115
Addiction—Discussion 2, 122, 125, 126
Adrenaline types—Phenanthrene series 73, 78
Alcoholic esters of morphine 10, 19
Alcoholic ethers of morphine 9, 17
Alcoholic hydroxyl configuration 14, 15, 16, 26
Alcoholic hydroxyl substitutions 9, 13, 18, 19, 20, 22, 23, 24
Aldehydes—Phenanthrene series 61
Alicyclic unsaturated linkages 26
Alkylation—Alcoholic hydroxyl 9, 17
Alkylation—Phenanthrene series 47
Alkylation—Phenolic hydroxyl 7, 8
Allopseudocodeine 5, 7, 15, 19, 21, 22, 23, 28
Amines, primary 55, 69, 74, 76, 78, 99
Amines, secondary 55, 69, 76, 78, 86, 99
Amines, tertiary 55, 69, 74, 76, 78, 86, 99
Amino alcohols—Carbazole series 106, 107, 108
Amino alcohols—Dibenzofuran series 99
Amino alcohols—Phenanthrene series 40, 73, 76, 79, 81, 85, 88, 92, 95
Aminocarbazoles 103, 109
Aminocodeine 29
Aminocodides 21, 24
Aminoketones—Dibenzofuran series 99
Aminoketones—Phenanthrene series 72

Page

Aminomorphides 21, 24
Aminomorphine 21, 29, 30
Aminophenanthrenes 51, 52, 54, 55
Amyldihydromorphinone 32, 33
Analgesia—Definition 6

Basic derivatives—Morphine series 21, 23, 34
Benzofuro-[2, 3-f]-quinoline 101
———, N-Methyl-1, 2, 3, 4-tetrahydro 101
———, 1, 2, 3, 4-Tetrahydro 101
Benzofuro-[3, 2-g]-quinoline 101
———, N-Methyl-1, 2, 3, 4-tetrahydro 101
———, 1, 2, 3, 4-Tetrahydro 101
Benzofuroquinolines 101
Benzyldihydrodesoxymorphine-D 8, 12
Benzyldihydromorphine 8, 27
Benzyl ethers, phenolic 8
Benzylmorphine 4, 8, 27
Benzylmorphine methyl ether 8
Blood pressure effects 8, 15
Bromocodeine 29, 30
14-Bromocodeinone 30, 31, 32
Bromocodide 12, 13, 23, 24
Bromomorphide 4, 12, 13, 23, 24
Bromomorphine 29

Carbazole 41, 103, 104, 109
———, 1-Amino 103, 104, 105
———, 3-Amino 103, 104, 105, 108
———, 6-Amino-1, 2, 3, 4-tetrahydro 106, 107, 108
———, 1-Hydroxy-1, 2, 3, 4-tetrahydro 106, 107, 108
———, 10-Hydroxy-1, 2, 3, 10-tetrahydro 106, 107, 108
———, 1-Keto-1, 2, 3, 4-tetrahydro 108
———, 3-Nitro 105
———, 1-Nitro-3, 6-dibromo 105
———, 9-Nitroso-3-nitro 105
———, 9-Acetyl:
———, ———, 3-Amino 103, 104, 105
———, 9-Ethyl:
———, ———, 3-Amino 103, 104, 105
———, 9-Methyl:
———, ———, 2-Acetyl 108
———, ———, 1-Amino 103, 104, 105
———, ———, 3-Amino 103, 104, 105
———, ———, 2-[2-(Diethyl-amino)-1-hydroxy-n-propyl] 107, 108
———, ———, 2-[3-(Dimethylamino)-1-hydroxy-n-propyl] 106, 107, 108
———, ———, 1-Nitro-3, 6-dibromo 105
Carbazole—Numbering system 103
Carbazole—Schematic relations 109
Carbinols—Dibenzofuran series 97
Carbinols—Phenanthrene series 61
Cardiac effect 90
Chemical structure and action—Conclusions 34, 69, 95, 102, 109, 110, 125

Page

Chemical structure and action—Discussion... 2, 37, 114
Chlorocodeine... 29, 30
α-Chlorocodide... 12, 13, 21, 23, 24, 27
β-Chlorocodide... 12, 13, 23, 28
Chlorodihydrocodide... 5, 11, 13, 21, 23, 27, 28
β-Chlorodihydrocodide... 13
8-Chlorodihydrocodide... 13
Chlorodihydromorphide... 5, 11, 13, 23, 27 28
α-Chloromorphide... 4, 12, 13, 21, 23, 24, 27
β-Chloromorphide... 4, 12, 13, 21, 23, 28, 121, 122, 123, 126
Chloromorphine... 29
Codeine... 4, 7, 8, 14, 18, 19, 23, 27, 30, 34, 121, 123, 125
Codeine isomers. *See* under Isomers.
Codeine methobromide... 33
Codeine methochloride... 34
Codeine methomethyl sulfate... 51
Codeine methyl ether... 9, 18, 27
Codeinone... 16
Convulsant action—Definition... 6
Curare-like action... 34
Cyclic amino alcohols... 88, 90, 92
Cyclic ketones... 92

Data, explanation of... 6, 42, 116
Dependence—Definition... 115
Depression, general—Definition... 6
Desocodeine. *See* Dihydrodesoxycodeine-D.
Desomorphine. *See* Dihydrodesoxymorphine-D.
Desoxycodeine-C... 5, 11, 12, 21, 22, 28
Desoxycodeines... 11
Desoxymorphine-C... 5, 11, 12, 21, 22, 28
Desoxymorphines... 11
Diacetyldihydrohydroxycodeine-B... 31
Diacetyldihydrohydroxycodeine-C... 31
Diacetyldihydromorphine... 27, 121, 125
Diacetylmorphine... 27
Diastereomers. *See* also Isomers... 4, 7, 14, 15
Dibenzofuran... 41, 97, 98, 102
———, 2-Acetyl... 97, 98
———, 3-Amino... 97, 98
———, 2-(2-Amino-1-hydroxy-ethyl)... 99, 100
———, 2-[2-(Diethylamino)-1-hydroxy-ethyl]... 99, 100
———, 2-[2-(Diethylamino)-1-oxo-ethyl]... 99, 100
———, 3-Dimethylamino... 97, 98
———, 2-[2-(Dimethylamino)-1-hydroxy-ethyl]... 99,100
———, 2-[2-(Dimethylamino)-1-oxo-ethyl]... 99, 100
———, 2-[2-(Ethylamino)-1-hydroxy-ethyl]... 99, 100
———, 2-Methyl carbinol... 97, 98
———, 2-(2-Piperidino-1-hydroxy-ethyl)... 99, 100
———, 2-Propionyl... 97, 98
———, 1, 2, 3, 4-Tetrahydro... 97, 98
———, ———, 7-Acetyl... 97, 98
———, ———, 7-[2-(Dimethylamino)-1-hydroxy-ethyl]... 99, 100
2-Dibenzofuran carboxylic acid... 97, 98
———, Methyl ester... 97, 98
Dibenzofuran—Comparison with Phenanthrene... 97, 100
Dibenzofuran—Numbering system... 97
Dibenzofuran—Schematic relations... 102
Dibenzofuran system in morphine... 25, 41
Dicodid. *See* dihydrocodeinone.
8-Diethylaminocodide... 23, 24
8-Diethylaminomorphide... 23, 24
Dihydroallopseudocodeine... 7, 15, 19, 20, 22, 25, 28

Page

Dihydrocodeine... 7, 14, 18, 19, 20, 22, 23, 27, 31, 32
Dihydrocodeine isomers. *See* under Isomers.
Dihydrocodeine methyl ether (same as Tetrahydrothebaine)... 18, 27, 121, 123, 125
Dihydrocodeinone... 16, 20, 24, 25, 31
Dihydrocodeinone enol acetate... 28, 32, 69, 121, 125
Dihydrodesoxycodeine-D... 11, 12, 21, 22, 28
Dihydrodesoxymorphine-D... 8, 11,12, 21, 22, 24, 25, 28, 121, 122, 126
Dihydroheterocodeine... 9, 14, 18, 27, 121, 122, 124, 126
Dihydrohydroxycodeine-A... 30, 31, 32
Dihydrohydroxycodeine-B... 30, 31, 32
Dihydrohydroxycodeine-C... 30, 31, 32
Dihydrohydroxycodeines... 29, 30
Dihydrohydroxycodeinone... 27, 29, 30, 69, 121, 122, 125
Dihydroisocodeine... 7, 14, 19, 20, 22, 23, 27, 31, 121, 125, 128
Dihydro-α-isomorphine... 7, 8, 14, 18, 20, 22, 23, 27, 121, 123
Dihydro-α-isomorphine alcoholic ethyl ether... 14, 18, 27
Dihydro-α-isomorphine alcoholic methyl ether... 14, 18, 27
Dihydro-β-isomorphine... 7, 15, 20, 22, 28
Dihydro-γ-isomorphine... 7, 8, 15, 20, 22, 25, 28
Dihydroisomorphinone... 16, 20
Dihydromorphine... 6, 8, 14, 18, 19, 20, 22, 23, 27, 32, 45
Dihydromorphine alcoholic ethyl ether... 14, 18, 27
Dihydromorphine isomers. See under Isomers.
Dihydromorphinone... 16, 20, 24, 32, 121, 122, 126
Dihydrophenanthrene derivatives... 40, 43, 54, 61, 70, 81, 95
Dihydropseudocodeine... 7, 15, 19, 20, 22, 25, 28
Dihydropseudocodeinone... 15, 16, 20
Dihydrothebaine... 16, 28
Dihydrothebainone... 25, 27
Dilaudid. *See* Dihydromorphinone.
Dionin. *See* Ethylmorphine.
Diphenylene oxide. *See* Dibenzofuran.
Di-substitution phenanthrene derivatives... 50, 64, 69

Emetic action—Definition... 6
Ephedrine types—Phenanthrene series... 76, 79
Esters (alcoholic) of morphine... 10, 19
Ethanolamines... 72, 81, 85
Ether oxygen bridge, opening of... 25, 34
Ethers of morphine... 7, 8, 9, 18
Ethylation—Morphine series... 8, 18
Ethyldihydro-α-isomorphine... 8, 27
Ethyldihydro-γ-isomorphine... 8, 28
Ethyldihydromorphinone... 32
Ethyl ethers, alcoholic... 18
Ethyl ethers, phenolic... 8
Ethyl-α-isomorphine... 8, 27
Ethyl-γ-isomorphine... 8, 28
Ethylmorphine... 4, 8
Eucodin. *See* Codeine methobromide.
Eukodal. *See* Dihydrohydroxycodeinone.
Exciting effect—Definition... 6

Habituation—Definition... 115
Halogenocodides... 5, 11, 12, 13, 21
Halogenomorphides... 4, 11, 12, 13, 21
Heart, effect on conduction in... 90
Heroin. *See* Diacetylmorphine.
Heterocodeine... 8, 9, 14, 18, 27

Page

Homologous derivatives — Phenanthrene series 61, 66, 92
Hydrogenation—Carbazole series 106, 107, 108
Hydrogenation—Dibenzofuran series 97, 98, 101
Hydrogenation—Morphine series 5, 11, 21, 26, 28, 29, 34
Hydrogenation—Phenanthrene series 40, 43, 54, 61, 81, 85, 88, 92
Hydroxyacetylphenanthrenes 63
Hydroxyaminophenanthrenes 58
14-Hydroxycodeine 30
Hydroxycodeinone 27, 29, 30
Hydroxyl, alcoholic. *See* Alcoholic hydroxyl.
Hydroxyl, phenolic. *See* Phenolic hydroxyl.
Hydroxyphenanthrenes 47, 48
Hydroxyphenanthrylene oxides 48

Intestinal effect 7, 15
Isocodeine 5, 7, 14, 19, 23, 27, 121, 123, 125
Isomerism, spatial 4, 15, 17, 34
Isomerism, structural 4, 15, 17, 34
Isomers of acetylcodeine 19
Isomers of acetylmorphine 10, 19
Isomers of chlorocodide 12, 19
Isomers of chlorodihydrocodide 13
Isomers of chloromorphide 12, 19
Isomers of codeine 4, 7, 14, 15
Isomers of dihydrocodeine 5, 7, 14
Isomers of dihydrocodeinone 16
Isomers of dihydrohydroxycodeine 30, 31, 32
Isomers of dihydromorphine 4, 5, 7, 14, 27, 28
Isomers of dihydromorphinone 16
Isomers of ethylmorphine 8, 17
Isomers of morphine 4, 5, 7, 14, 15, 27, 28
Isomers—Phenanthrene series 47, 48, 52, 55, 58, 61, 63, 66, 69, 73, 76, 88, 90
Isomethyldihydrocodeinone 30
α-Isomorphine 4, 5, 7, 8, 14, 18, 19, 23, 27, 121, 123, 125
α-Isomorphine alcoholic ethyl ether 14, 18, 27
α-Isomorphine alcoholic methyl ether 14, 18, 27
β-Isomorphine 4, 5, 7, 15, 19, 21, 22, 23, 28
γ-Isomorphine 4, 5, 7, 8, 15, 18, 19, 21, 22, 23, 28
γ-Isomorphine alcoholic ethyl ether 6, 18
γ-Isomorphine alcoholic methyl ether 5, 9, 18
Isonitrosoacetylphenanthrenes 75
Isopropyldihydromorphinone 32
Isoquinoline, 6,7-Diethoxy-1-(3′, 4′-diethoxybenzyl) 125, 127
Isoquinoline system in morphine 39

Ketones—Dibenzofuran series 99
Ketones—Morphine series 16, 20, 32
Ketones—Phenanthrene series 61, 63, 64, 72

Methods of study iii, 1, 39, 40, 42, 104, 114, 116
Methoxymethyldihydromorphine 8
Methylation—Morphine series 7, 18
Methyldihydrocodeine 20, 30, 32
Methyldihydrocodeinone 20, 30, 32
Methyldihydrocodeinone enol acetate 32
Methyldihydromorphine 20, 30, 32
Methyldihydromorphinone 20, 30, 32, 33, 121, 122, 123, 126, 127
Methyl ethers, alcoholic 9, 18
Methyl ethers, phenolic 8
Methylmorphenol 48, 51
α-Methylmorphimethine 51

Page

β-Methylmorphimethine 51
β-Methylmorphimethine methomethylsulfate 51
ε-Methylmorphimethine 6
Methylmorphine. *See* Codeine.
Monoacetyl dihydromorphine 10, 19, 27
Monoacetyl-α-isomorphine 10, 19
Monoacetyl-β-isomorphine 10, 19
Monoacetyl-γ-isomorphine 10, 19
Monoacetylmorphines 10, 19, 27
Monohydroxyphenanthrenes 47
Morphenol 41, 48, 49, 51
Morphigenine (Vahle's) 58, 60, 61
Morphine 2, 4, 7, 8, 14, 18, 19, 23, 27, 30, 34, 39, 45, 51, 59, 69, 114, 118, 121, 122, 123, 124
Morphine alcoholic ethyl ether 14, 18, 27
Morphine alcoholic methyl ether. *See* Heterocodeine.
Morphine esters 4, 10, 19
Morphine ethers 4, 7, 8, 9, 18
Morphine isomers. *See* under Isomers.
Morphine-like effect—Carbazole series 104
Morphine-like effect—Phenanthrene series 74, 94
Morphine methochloride 34
Morphine—Numbering system 4
Morphine sulfonic acids 29
Morphol 48, 49
Muzzling, alcoholic hydroxyl 17, 34
Muzzling, phenolic hydroxyl 7, 8, 34
Muzzling hydroxyl—Phenanthrene series 48, 49, 69, 74, 79, 88

Naphthalene 46, 65, 70
β-(1-Naphthoyl)-propionic acid 46
β-(2-Naphthoyl)-propionic acid 46
γ-(1-Naphthyl)-n-butyric acid 46
γ-(2-Naphthyl)-n-butyric acid 46
Nitrocodeine 29
Nitrogen, modification of 33, 34
Nitrosomorphine 29
Novocaine types 67
Nuclear substitutions—Morphine series 20, 29, 30, 31, 32, 34
Numbering systems 4, 40, 97, 103

Octahydrophenanthrene derivatives 40, 43, 61, 63, 70, 85, 95
Oestrogenic activity 65

Peronin. *See* Benzylmorphine.
Perparin 125, 127
Phenanthrene 40, 43, 45, 53, 70, 96
———, 2-Acetoxy 47
———, 3-Acetoxy 47
———, 2-Acetyl 61, 62
———, 3-Acetyl 61, 62, 64
———, 9-Acetyl 61, 62, 64
———, 3-(Acetylamino) 52
———, 3-Aldehyde 61, 62
———, 9-Aldehyde 61, 62
———, 2-Amino 52, 56
———, 3-Amino 52, 56, 60
———, 9-Amino 52, 60
———, 3-(2-Amino-1-hydroxy-ethyl) 73, 74, 75, 100
———, 3-(2-Amino-1-hydroxy-n-propyl) 76, 78, 79
———, 9-(Aminomethyl) 52, 53
———, 9-Bromo 53, 68
———, 3-Carbinol 61, 62
———, 9-Carbinol 61, 62

Page

Phenanthrene, 9-Cyano 53, 62, 68
———, 3, 4-Diacetoxy 48
———, 3, 6-Diacetoxy 48, 50
———, 3-[2-(Diethylamino)-1-hydroxy-ethyl] 73, 74, 75, 100
———, 3-[2-(Diethylamino)-1-hydroxy-n-propyl] 76, 78, 79
———, 3-[3-(Diethylamino)-1-hydroxy-n-propyl] 77, 78, 79
———, 3-[2-(Diethylamino)-1-oxo-ethyl] 72, 74, 75
———, 3, 4-Dihydroxy 48, 49
———, 3, 6-Dimethoxy-4-acetoxy 48, 50
———, 3-Dimethylamino 52, 53
———, 3-[2-(Dimethylamino)-1-hydroxy-ethyl] 73, 74, 75, 100
———, 9-[2-(Dimethylamino)-1-hydroxy-ethyl] 73, 74, 75
———, 3-[2-(Dimethylamino)-1-hydroxy-n-propyl] 76, 78, 79
———, 3-[2-(Dimethylamino)-1-oxo-ethyl] 72, 74, 75, 100
———, 2-Ethoxy 47
———, 3-Ethoxy 47
———, 9-Ethoxy-10-acetylamino 58, 60
———, 3-[2-(Diethylamino)-1-acetoxy-ethyl] 73, 74, 75
———, 3-[2-(Ethylamino)-1-hydroxy-n-propyl] 76, 78, 79
———, 1-Hydroxy 47
———, 2-Hydroxy 47
———, 3-Hydroxy 47, 49, 60, 64
———, 4-Hydroxy 47
———, 9-Hydroxy 47, 48, 60, 64
———, 3-Hydroxy-6-acetyl 63, 64, 65
———, 9, Hydroxy-10-acetyl 63, 64, 65
———, 9-Hydroxy-10-Acetylamino 58, 60
———, 3-Hydroxy-4-amino 58, 60
———, 3-Hydroxy-9-amino 58, 60
———, 9-Hydroxy-10-amino 58, 60, 61
———, 3-Hydroxy-6-[2-(diethylamino)-1-acetoxy-ethyl] 79, 80
———, 3-Hydroxy-6-[2-(diethylamino)-1-hydroxy-ethyl] 79, 80
———, 2-Methoxy 47
———, 3-Methoxy 47, 64, 68
———, 3-Methoxy-6-acetyl 63, 64, 65
———, 3-Methoxy-9-acetyl 63, 64, 65
———, 9-Methoxy-10-acetylamino 58, 60
———, 3-Methoxy-9-amino 58, 60
———, 9-Methoxy-10-amino 58, 60
———, 3-Methoxy-9-diacetylamino 58, 60
———, 3-Methoxy-9-[2-(dimethylamino)-1 hydroxy-ethyl] 79, 80
———, 2-Methyl carbinol 61, 62, 63
———, 3-Methyl carbinol 61, 62, 63
———, 9-Methyl carbinol 61, 62, 63
———, 3-(2-Piperidino-1-hydroxy-ethyl) 24, 73, 74, 75, 100
———, 3-(3-Piperidino-1-hydroxy-n-propyl) 77, 78, 79
———, 3-(2-Piperidino-1-oxo-ethyl) 72, 74, 75
———, 3-Propionyl 61, 62
———, 3-[3-(1, 2, 3, 4-Tetrahydroisoquinolino)-1-hydroxy-n-propyl] 77, 78, 79
———, 9, 10-Dihydro 40, 43, 44
———, ———, 2-Acetyl 56, 61, 62
———, ———, 2-Amino 54, 56

Page

Phenanthrene, 9, 10-Dihydro, 2-[2-(Diethylamino)-1-acetoxyethyl] 81, 83
———, ———, 2-[2-(Diethylamino)-1-hydroxy-ethyl] 81, 83
———, ———, 2-[2-(Diethylamino)-1-hydroxy-n-propyl] 82, 83
———, ———, 2-[2-(Diethylamino)-1-oxo-ethyl] 81, 83
———, ———, 2-Dimethylamino 54, 56, 57
———, ———, 2-[2-(Dimethylamino)-1-acetoxy-ethyl] 81, 83
———, ———, 2-[2-(Dimethylamino)-1-hydroxy-ethyl] 81, 83
———, ———, 2-(2-Piperidino-1-acetoxy-ethyl) 81, 83
———, ———, 2-(2-Piperidino-1-hydroxy-ethyl) 81, 83
———, ———, 2-(2-Piperidino-1-hydroxy-n-propyl) 82, 83
———, ———, 2-[2-(1, 2, 3, 4-Tetrahydroisoquinolino)-1-acetoxy-ethyl] 81, 83
———, ———, 2-[2-(1, 2, 3, 4-Tetrahydroisoquinolino)-1-hydroxy-ethyl] 81, 83
———, ———, 2-[2-(1, 2, 3, 4-Tetrahydroisoquinolino)-1-hyroxy-n-propyl] 82, 83
———, (Cis, trans) 1, 2, 3, 4, 9, 10, 11, 12-Octahydro 45
———, (Sym.) 1, 2, 3, 4, 5, 6, 7, 8-Octa-hydro 40, 43, 44
———, ———, 9-Acetyl 61, 62, 87
———, ———, 9-[2-(Diethylamino)-1-hydroxy-ethyl] 85, 87
———, ———, 9-[2-(Dimethylamino)-1-hydroxy-ethyl] 85, 87
———, ———, 9-[2-(Dimethylamino)-1-hydroxy-n-propyl] 86, 87
———, ———, 9-[2-(Ethylamino)-1-hydroxy-n-propyl] 86, 87
———, ———, 1-Keto 63, 64, 65
———, ———, 1-Oxo 63, 64, 65
———, ———, 9-(2-Piperidino-1-hydroxy-ethyl) 85, 87
———, ———, 9-(2-Piperidino-1-hydroxy-n-propyl) 86, 87
———, ———, 9-Propionyl 61, 62
———, 1, 2, 3, 4-Tetrahydro 43, 44, 46
———, ———, 1-Amino 55, 56, 57
———, ———, 4-Amino 55, 56, 57
———, ———, 3-Diethylamino-4-hydroxy 88, 90
———, ———, 3-[(Diethylamino)-methyl]-4-hydroxy 92, 93, 94
———, ———, 3-[(Diethylamino)-methyl]-4-oxo 92, 93, 94
———, ———, 1-Dimethylamino 55, 56
———, ———, 4-Dimethylamino 55, 56
———, ———, 2-(Dimethylamino)-1-hydroxy 88, 90
———, ———, 3-(Dimethylamino)-4-hydroxy 88, 90
———, ———, 9-[2-(Dimethylamino)-1-hydroxy-n-propyl] 86, 87
———, ———, 1-Keto 46, 57, 63, 64, 65, 93, 94
———, ———, 4-Keto 46, 57, 63, 64, 65, 93, 94
———, ———, 1-Methylamino 55, 56
———, ———, 1-Oxo (Oxime) 57, 63, 64, 65
———, ———, 4-Oxo (Oxime) 57, 63, 64, 65
———, ———, 2-Piperidino-1-hydroxy 88, 90
———, ———, 3-Piperidino-4-hydroxy 88, 90
———, ———, 2-(Piperidino-methyl)-1-hydroxy 93, 94

Page

Phenanthrene, 1, 2, 3, 4-Tetrahydro, 2-(Piperidino-methyl)-1-oxo 93, 94
———, ———, 3-(1, 2, 3, 4-Tetrahydroisoquinolino)-4-acetoxy 88, 90
———, ———, 2-(1, 2, 3, 4-Tetrahydroisoquinolino)-1-hydroxy 88, 90
———, ———, 3-(1, 2, 3, 4-Tetrahydroisoquinolino)-4-hydroxy 88, 90, 125, 127
———, ———, 3-[(1, 2, 3, 4-Tetrahydroisoquinolino)-methyl]-4-hydroxy 93, 94
Phenanthrene-2-carboxylic acid 66, 67, 68
———, Amide 66, 68
———, Methyl ester 66, 68
Phenanthrene-3-carboxylic acid 66, 67, 68
———, Amide 66, 68
———, β-(Diethylamino)-ethyl ester 66, 67, 68
———, Dimethyl amide 66, 68
———, Methyl ester 66, 68
Phenanthrene-9-carboxylic acid 66, 67, 68
———, Amide 66, 68
———, β-(Diethylamino)-ethyl ester 66, 67, 68
———, 3-Methoxy 66, 68
———, Methyl ester 66, 68
———, 1, 2, 3, 4, 5, 6, 7, 8-Octahydro 66, 68
Phenanthrene-3-propionic acid 66, 68, 69
———, Amide 66, 68, 69
———, Methyl ester 66, 68, 69
Phenanthrene—Absorption of 44
Phenanthrene—Comparison with carbazole 97
Phenanthrene—Comparison with dibenzofuran 97, 100
9-Phenanthrone, 10, 10-Dichloro 48
Phenanthrenedisulfonate 50
Phenanthrene methyl alcohols. *See* Phenanthrene carbinols.
Phenanthrene—Numbering system 40
3, 4-Phenanthrene quinone 49
9, 10-Phenanthrene quinone 48
9, 10-Phenanthrene quinone monoxime 61
Phenanthrene—Schematic relations 70, 95
3-Phenanthrene sulfonic acid 50
Phenanthrene system in morphine 2, 39, 45
Phenanthroic acids. *See* Phenanthrene carboxylic acids.
Phenanthrols. *See* Hydroxyphenanthrenes.
β-(2-Phenanthryl)-acrylic acid 69
β-(3-Phenanthryl)-acrylic acid 69
4, 5-Phenanthrylene oxide 25, 41, 48
———, 3-Acetoxy 48, 51

Page

4, 5-Phenanthylene oxide, 3-Hydroxy 41, 48, 49, 51
———, 3-Methoxy 48, 51
Phenanthrylene oxide system in morphine 25
Phenolic ethers of morphine 7, 8
Phenolic hydroxyl substitutions 4, 7, 8, 9, 10, 12, 13
Physical properties and action 37
Piperidino-ethanol 24
8-Piperidocodide 6, 23
6-Piperidodihydromorphide 23, 24, 27
6-Piperidomorphide 23, 24, 27
8-Piperidomorphide 23, 24
Polyhydroxyphenanthrenes 48
Propanolamines 76, 82, 86
Pseudocodeine 5, 7, 18, 19, 21, 22, 23, 28, 121, 123, 125
Pseudocodeine methyl ether 6, 9, 18
Pseudocodeine phenyl ether 18
Pseudocodeinone 6, 15, 16
Pseudomorphine 27
Pyridino-dibenzofurans. *See* Benzofuroquinolines.

Quarternary alkylates 33, 34

Respiratory effect—Definition 6

Schematic relations—Carbazole series 109
Schematic relations—Dibenzofuran series 102
Schematic relations—Phenanthrene series 70, 95

Tetrahydroallopseudocodeine 22, 25
Tetrahydrocarbazole derivatives 106, 107, 108
Tetrahydrodesoxycodeine 11, 12, 21, 22, 25
Tetrahydrodesoxymorphine 6, 11, 12, 21, 22, 25
Tetrahydrodibenzofuran derivatives 97, 98, 101
Tetrahydro-γ-isomorphine 21, 22, 25
Tetrahydroisoquinoline derivatives 77, 81, 88, 93
Tetrahydromorphine derivatives 5, 12, 22, 25
Tetrahydrophenanthrene derivatives 43, 55, 63, 70, 86, 88, 92, 95
Tetrahydropseudocodeine 21, 22, 25
Tetrahydropseudomorphine 27
Tetrahydrothebaine (Same as Dihydrocodeine methyl ether) 10, 18, 27, 28
Thebaine 29, 30, 31, 50
Thebainone 27
Tolerance—Definition 115
Toxicity—Definition 6

Veratrine-like effect 67